Asymmetric Lactam Synthesis

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

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Declaration

All of the work carried out in this thesis is original research work carried out at the University of Warwick between October 2009 and May 2013. I declare that the material described that is not original has been identified and appropriately referenced. I certify that the material within this thesis has not been submitted for a degree at any other university.

Abstract

Broad-Spectrum Chemokine Inhibitors (BSCIs) are a novel type of anti-inflammatory drug, discovered by Fox and colleagues. We have shown that the syntheses of C-substituted γ-thialactams are possible *via* a modular approach starting from the simple amino acid cystine. These compounds are a new class of GPCR ligand, showing BSCI activity comparable to their non-sulfur counterparts. Initial migratory data suggests that these lactams are inhibitors of leukocyte migration and comparable to the analogous BSCI lactams at μM concentrations, with decreased activity at the nM scale.

Efforts have been made to the synthesis of substituted piperidinones, as well as employing Jocic-Reeve-Corey-Link chemistry to the general synthesis of lactams, ultimately looking to the synthesis of C-substituted lactams. Attempting to utilise trichloromethyl carbinol chemistry for these purposes has led to the synthesis of stereochemically-pure heterocycles containing up to 3 stereocentres. α-Trichloromethyl carbinols and asymmetric transfer hydrogenation chemistry are used from simple starting materials. Developments of this type of chemistry will undoubtedly lay the foundations to produce further non-racemic substituted heterocycles which will be important both synthetically and biologically.

Abbreviations

General

μM – Micromolar

7TM – 7-Transmembrane

ACE – Angiotensin-converting enzyme

aq – aqueous

Ar - Aryl

ATH – Asymmetric transfer hydrogenation

Bn – Benzyl

Boc – Di-*tert*-butyl dicarbonate

BOP – Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate

BSCI – Broad spectrum chemokine inhibitor

Bu – Butyl

CBS – Corey-Bakshi-Shibata

Cbz – Carboxybenzyl

CGRP – Calcitonin gene related peptide

cm^{-1} – centimetre

CNS – Central nervous system

COPD – Chronic obstructive pulmonary disease

COX – Cyclooxygenase

DCC – *N*,*N*'-Dicyclohexylcarbodiimide

DCM – Dichloromethane

DME - Dimethoxyethane

DMF – Dimethylformamide

DMP – Dess-Martin periodinane

DMSO – Dimethyl sulfoxide

DPEN – 1,2-Diphenyl-1,2-ethylenediamine

e.e. – enantiomeric excess

ED_{50} – Median effective dose

EDCI – 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

Et – Ethyl

EtOAc – Ethyl acetate

Fmoc – Fluorenylmethyloxycarbonyl

FP – Fluorescence polarisation

g – grams

GDP – Guanosine diphosphate

GH – Growth hormone

GHIH – Growth hormone inhibiting hormone

GPCR – G-protein coupled receptor

GTP – Guanosine triphosphate

h_{υ} – Luminous exposure

HIV – Human immunodeficiency virus

i- – ipso

IBX – 2-Iodoxybenzoic acid

ICE – Interleukin-1 converting enzyme

IL – Interleukin

ImSAID – Immune selective anti-inflammatory drug

IR - Infrared

m- – meta

MCP – Monocyte chemotactic protein

m-cpba – *meta*-Chloroperoxybenzoic acid

ME - Mercaptoethanol

Me – Methyl

Me – Methyl

MIP – Macrophage inflammatory protein

mmol - Millimole

mol - Mole

Ms – Mesyl

NBS – *N*-Bromosuccinimide

NEt_3 – Triethylamine

NHS – *N*-Hydroxysuccinimide

nM – Nanomolar

NMM – *N*-Methylmorpholine

NMR – Nuclear magnetic resonance

NSAID – Non-steroidal anti-inflammatory drug

o- – ortho

^oC - Celcius

org – organic

p- – para

PG – Protecting group

Ph – Phenyl

Phth – Phthalimide

pKa – Negative logarithm of the acid dissociation constant

pM – Picomolar

ppm – Parts per million

PPTS – Pyridinium *para*-toluenesulfonate

Pr – Propyl

PTC – Phase transfer catalyst

p-TSA – *para*-Toluenesulfonic acid

RT – Room temperature

SAR – Structure activity relationship

S_N1 – Unimolecular nucleophilic substitution

S_N2 – Bimolecular nucleophilic substitution

SRIF – Somatotropin release inhibiting factor

SSTR – Somatostatin receptor

TBAB – Tetra-n-butylammonium bromide

TBAF – Tetra-n-butylammonium fluoride

^{t}Bu – *tert*-Butyl

TFA – Trifluoroacetic acid

THF – Tetrahydrofuran

TLC – Thin layer chromatography

TMS – Trimethylsilyl

TNF – Tumor necrosis factor

TsDPEN – *N*-Tosyl-1,2-Diphenyl-1,2-ethylenediamine

Δ – Heat

Amino Acids

A – Ala – Alanine

C – Cys – Cysteine

D – Asp – Aspartic acid

E – Glu – Glutamic acid

F – Phe – Phenylalanine

G – Gly – Glycine

H – His – Histidine

I – Ile – Isoleucine

K – Lys – Lysine

L – Leu – Leucine

M – Met – Methionine

N – Asp – Asparagine

P – Pro – Proline

Q – Gln – Glutamine

R – Arg – Arginine

S – Ser – Serine

T – Thr – Threonine

V – Val – Valine

W – Trp – Tryptophan

Y – Try – Tyrosine

Chapter 1 - Introduction

1.1 Inflammation

Inflammation is a biological and protective response of living tissue to harmful stimuli. A more precise definition from Stedman's medical dictionary is "A fundamental pathologic process consisting of a dynamic complex of histologically apparent cytologic changes, cellular infiltration, and mediator release that occurs in the affected blood vessels and adjacent tissues in response to an injury or abnormal stimulation caused by a physical, chemical, or biologic agent, including the local reactions and resulting morphologic changes; the destruction or removal of the injurious material; and the responses that lead to repair and healing."[1] The classic signs and symptoms of acute inflammation are *rubor* (redness), *calor* (heat or warmth), *tumor* (swelling), *dolor* (pain) and *functio laesa* (inhibited or lost function).[2-5]

Inflammation is vital in initiating the healing process - in its absence wounds and infections would never heal and progressive destruction of the tissue would compromise the survival of the organism. Although this process serves to protect its host, if kept uncontrolled inappropriate inflammatory response can contribute to a wide range of disorders and diseases including: autoimmune,[6-9] Alzheimer's,[10-12] cancer,[13-15] arthritis[16-17] and many others.

1.1.1 Inflammation Mechanism

The inflammation mechanism, although very complex, exhibits a certain order of events (**Figure 1**), beginning with tissue injury followed by the release of chemicals and leukocyte (white blood cell) migration.[18-21] When tissue cells

become injured they release a number of chemicals (for example kinins, prostaglandins and histamine**)** that initiate the inflammatory response. These chemicals work together, causing dilation of blood vessels and permeability of the capillaries which in turn increases the blood flow to the injured site. These substances also act as chemical messengers that attract some of the body's natural defence cells, a mechanism known as chemotaxis. Chemotaxis leads to the migration of leukocytes. During an inflammatory response, two types of leukocytes are predominant - macrophages and neutrophils. Macrophages, the largest of the leukocytes, aid the healing process by engulfing bacteria and dead cells and ingesting them so that the area is clear for new cells to grow. Neutrophils are first to the injured site and function by neutralising harmful bacteria. Their activity and death in large numbers usually results in the formation of pus. Angiogenesis, the formation of new blood vessels, occurs once sufficient cleansing of the area has been achieved, followed by a proliferation and remodeling phase.[22-24]

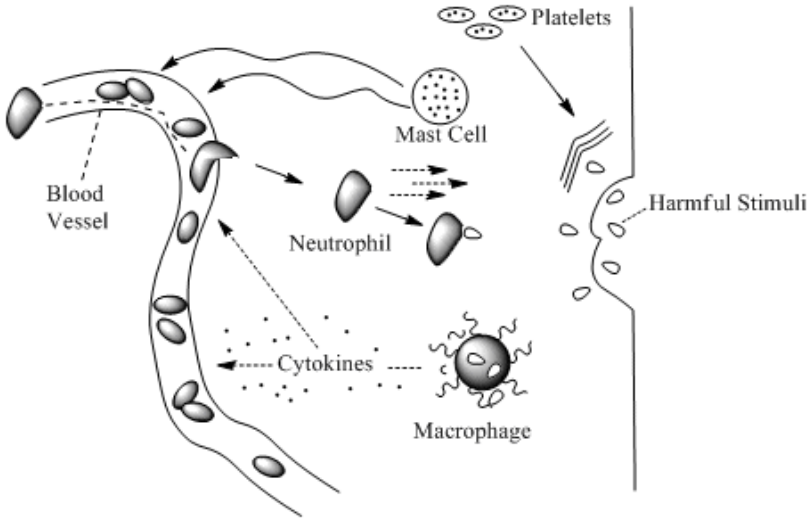


Figure 1. Common inflammatory and immune processes. Bacteria and other pathogens enter the wound and platelets release blood clotting proteins to the site. Vasodilation is activated by mast cells delivering blood, plasma and cells to the injured site. Neutrophils and macrophages kill and degrade pathogens, while macrophages release cytokines that attract immune system cells to the injured site for repair. Inflammation ceases when the pathogen is eliminated and the wound repaired. (Reproduced and altered from *Molecular biology in medicinal chemistry*)[24]

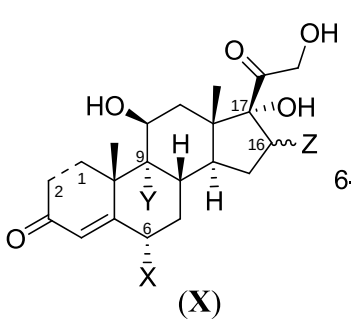
1.1.2 Treatment of Inflammation

There are a number of ways to treat inflammation. Ice and cold water have long been associated with the treatment of inflammation, although it probably helped to suppress the pain of the inflammation rather than to treat the problem directly.[25] It has been recognised that lifestyle and environment play an important role in inflammatory responses - a recent study has found that certain dietary components can play an important role in the treatment of inflammation.[26] Other natural anti-inflammatory agents have been used and are available in many forms such as topical applications (like creams and lotions), supplements, herbal extracts and natural oils.[27] Suffice to say, the most widely used treatment of inflammatory diseases and disorders in use today are anti-inflammatory agents which are classified into three groups: steroidal, non-steroidal and immune-selective. Four of the top ten pharmaceutical products in 2011 were anti-inflammatory agents, with global sales figures exceeding £18 billion.[28]

1.1.2.1 Steroid Anti-Inflammatory Drugs - Glucocorticoids

For more than 50 years the beneficial effects of glucocorticoids in the treatment of inflammatory diseases have been appreciated.[29] Unfortunately, they have been fraught with serious complications which have imposed limitations on the clinical use of this class of drugs.[30] Nevertheless, these steroids, often referred to as corticosteroids, have been used in the treatment of diseases such as asthma, rheumatoid arthritis, inflammatory bowel disease and autoimmune disorders.[2,10,12,16,31-33] They are a group of naturally occurring steroids produced in the adrenal cortex and work by down-regulating the gene expression of inflammatory mediators.[34-35] Arguably the best known and most important natural glucocorticoid Cortisol (**1.1**), or hydrocortisone, is essential for life. A considerable research effort has been devoted to the structural modifications of glucocorticoids, with the hope of increasing their potencies while minimising their propensity to elicit systemic adverse effects. For instance, introduction of a Δ^{1-2}

double bond and modifications to the -6,-9, -16 and -17 positions of the rings have all given positive results (**Figure 2**).[30,36-46]



(X)	Δ^{1-2}	X	Y	Z
Hydrocortisone (**1.1**)	S	H	H	H
Fludrocortisone (**1.2**)	S	H	F	H
Prednisolone (**1.3**)	U	H	H	H
6-Methylprednisolone (**1.4**)	U	Me	H	H
Triamcinolone (**1.5**)	U	H	F	(*S*)-OH
Dexamethasone (**1.6**)	U	H	F	(*S*)-Me
Betamethasone (**1.7**)	U	H	F	(*R*)-Me

Figure 2. The glucocorticoids motif (left) and related drugs from certain modifications as shown in the table (right). (Note: Δ^{1-2} are either unsaturated (U) or saturated (S))

Seretide (**Figure 3**), the 3rd best selling drug globally with sales of £5.5 billion in 2011,[28] is used in the management of asthma and chronic obstructive pulmonary disease (COPD) and contains fluticasone (**1.8**), a corticosteroid.[47] This anti-inflammatory component is combined with salmeterol (**1.9**) to clear the lungs, airways and relieve the symptoms of coughing, wheezing and shortness of breath.

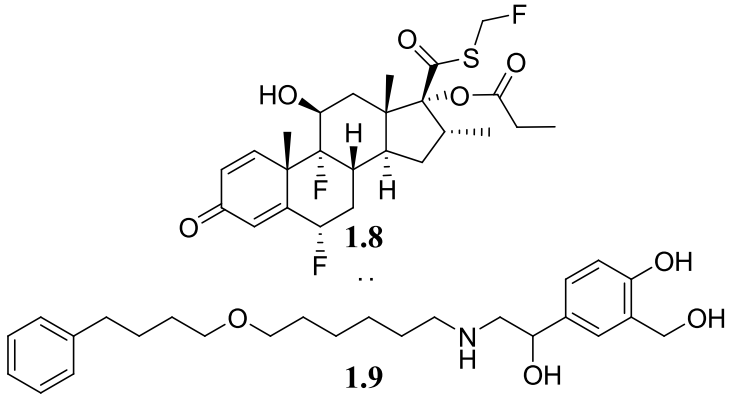
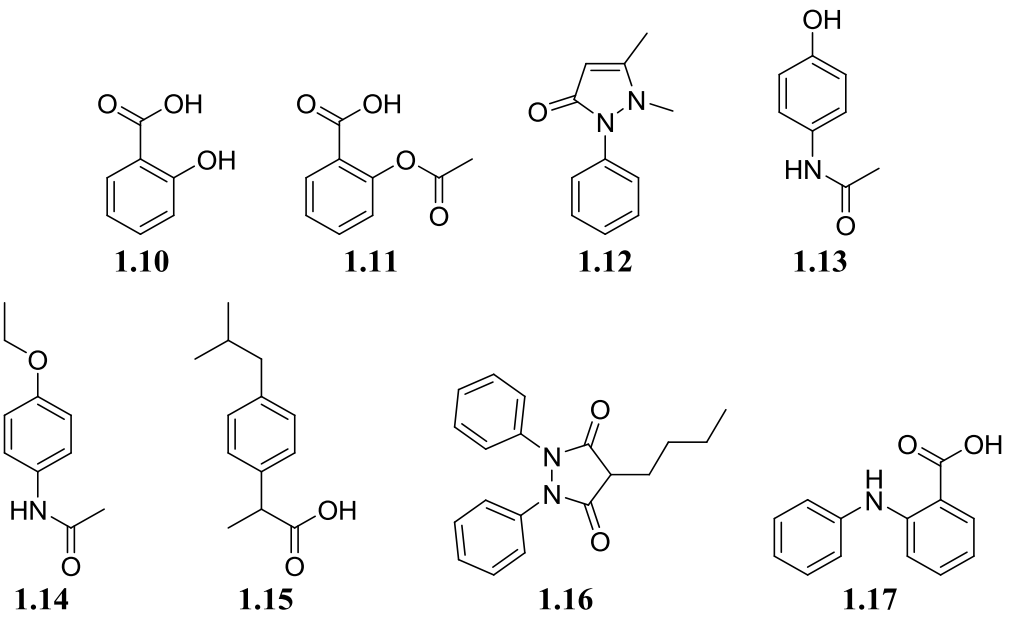


Figure 3. The drug Seretide which contains fluticasone (**1.8**) and salmeterol (**1.9**).

1.1.2.2 Non-Steroid Anti-Inflammatory Drugs (NSAIDs)

The main therapeutic actions of salicylic acid (**1.10**)[48] and its derivatives, such as aspirin (**1.11**), have long been recognised.[49-51] With the passing of time, several other drugs were discovered that shared some or all of their antipyretic, anti-inflammatory, and analgesic effects. These include phenazone (**1.12**), paracetamol

(**1.13**), phenacetin (**1.14**), ibuprofen (**1.15**), phenylbutazone (**1.16**), and, more recently, the fenamates (derived from fenamic acid (**1.17**)).[52-54]



Despite the diversity of their chemical structures, these drugs all share the same therapeutic properties and were thus regarded as the aspirin-like drugs. Today the term 'nonsteroidal anti-inflammatory drugs' (NSAIDs) is more generally used, as they are quite clearly distinct from the steroidal structures of the glucocorticoids (*vide supra*) but produce similar anti-inflammatory effects. Unfortunately, these types of drugs also have their drawbacks. All of the NSAIDs are approximately equivalent in terms of anti-inflammatory efficacy but can also cause untoward side effects (e.g. gastrointestinal and renal adverse drug reactions) in a significant fraction of treated patients, which has frequently limited their use in therapy.

Most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase (COX).[17] This enzyme is involved in the biosynthesis of prostaglandins (PGs) and thromboxane A_2 (TXA_2) from arachidonic acid (**Figure 4**), agents which are responsible for the body's response to pain and inflammation.[22b] Inhibiting the enzyme lowers prostaglandin levels and alleviates these symptoms.[35,55-57]

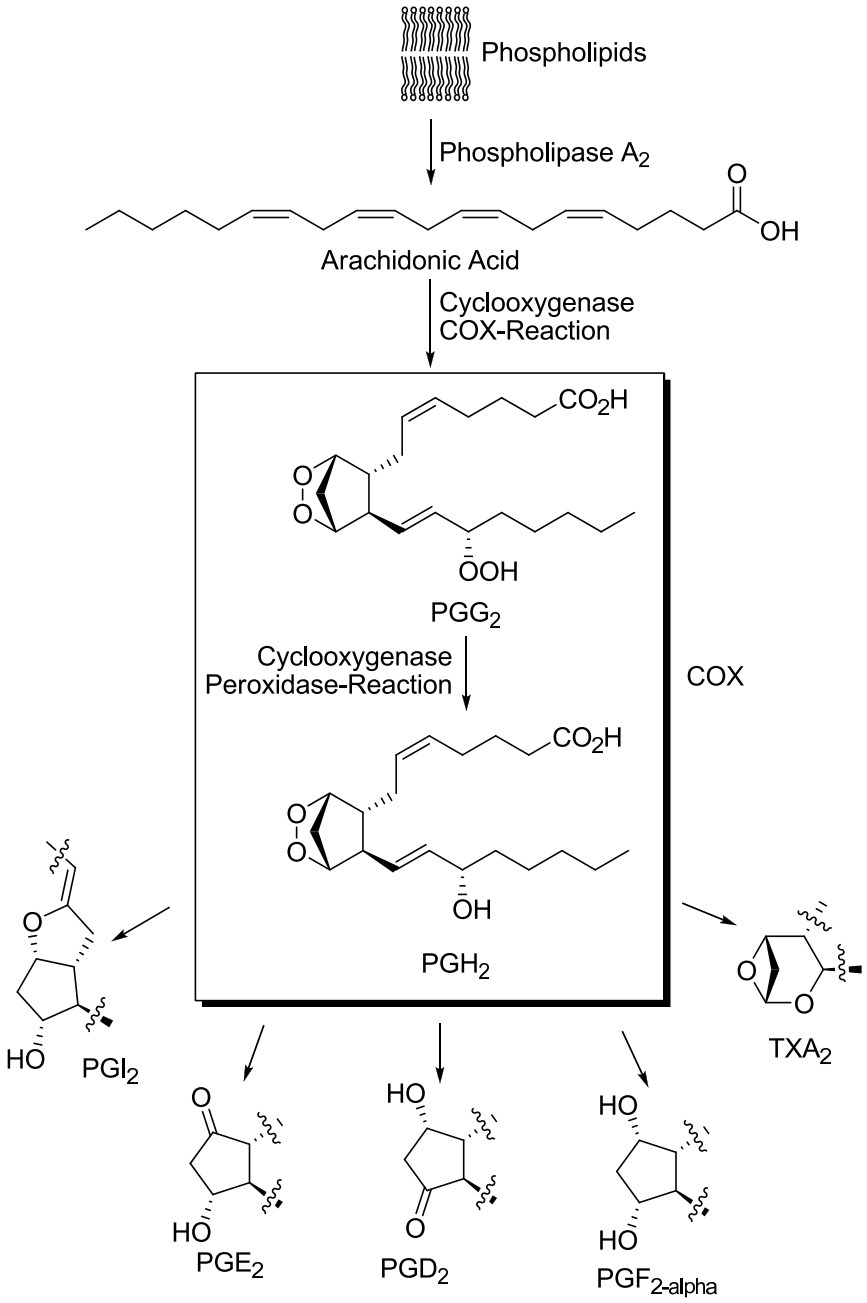
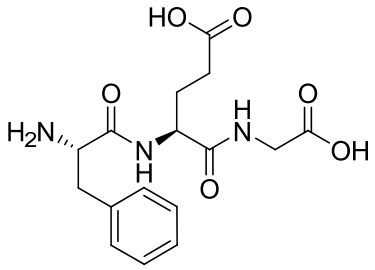


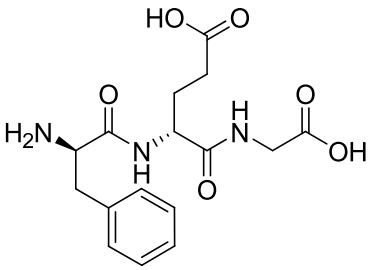
Figure 4. Biosynthesis of prostaglandins from arachidonic acid *via* COX enzymes.

1.1.2.3 Immune Selective Anti-Inflammatory Derivative (ImSAIDs)

ImSAIDs are a new category of anti-inflammatory drug which are unrelated to steroids or NSAIDs. They are a class of peptides, or amino acid complexes, that aid in reducing over-activation of leukocytes and thus help support anti-inflammatory activity, a function which is not performed by conventional NSAIDs and glucocorticoids.[58-59]



FEG (**1.18**)



feG (**1.19**)

The current lead ImSAID contains the three amino acid sequence FEG (**1.18**). This has become the foundation for this category of drug, along with its *D*-enantiomeric form feG (**1.19**).[60] It is now well accepted that the immune, nervous and endocrine systems communicate and interact to control and modulate inflammation and tissue repair.[61]

1.2 Chemokines

During leukocyte extravasations, the movement of leukocytes out of the circulatory system towards the site of tissue damage or infection, resident macrophages in the affected tissue release cytokines (*vide infra*) such as IL-1, TNF-α and chemokines. Targeting leukocyte recruitment to abolish inappropriate inflammation is therefore an attractive therapeutic strategy, and has recently become an important focus for anti-inflammatory drug design.[62-66] One of the best studied examples is the chemokine system, with chemokine inhibitiors proving to be novel anti-inflammatory drugs, although care has to be taken to balance the inhibition as chemokines also have a beneficial role on the immune system.

1.2.1 Chemokine Classification

Chemokines are a family of structurally related small proteins secreted by the cell that exhibit very specific cysteine motifs in their amino acid sequence. The approximately 50 chemokines and 19 receptors identified to date are classified

into four families on the basis of the pattern of the first two of four cysteine residues of the ligand, given the preferred names CXC, CC, C, and CX3C. Less commonly, these groups are referred to by the Greek letters α, β, γ and δ respectively.[67]

CXC, CC, and CX3C chemokines all have four conserved cysteines, whereas C chemokines have only two, corresponding to the second and fourth cysteines in the other classes. The CXC family is characterised by the presence of a single amino acid residue between the first two cysteines, whereas the large CC chemokine family consists of chemokines with the first two cysteine residues adjacent to each other (it should be noted that there is a small subgroup of CC chemokines which have six cysteine residues). Analogously, the CX3C chemokines contain three amino acid residues between the first two cysteines (**Figure 5**).[67-69]

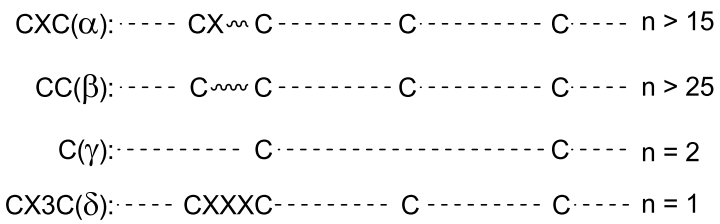


Figure 5. Classification of each chemokine family. C indicates the cysteine residue; X, an amino acid other than cysteine; ---, other amino acids; and ~, gaps in the alignment. The number of members in each class is listed on the right. Spacing between cysteines is similar with the N and C terminus varying in length.

Both the CC and CXC groups have many known members, with examples including macrophage inflammatory protein (MIP-1α or CCL3), monocyte chemotactic protein (MCP-1 or CCL2) and Interleukin-8 (IL-8 or CXL8). Human lymphotactin α and β, and fractalkine and their equivalents in other species are the only known examples of C and CX3C chemokines respectively.

1.2.2 Chemokine Receptors

To the best of our knowledge there are now 19 chemokine receptors (summarised in **Table 1**).[68-70] These chemokines signal through type 1 G-protein coupled receptors (GPCRs) to regulate a range of immune functions: wound healing, lymphoid trafficking, lymphoid organ development, inflammation, cell recruitment, metastasis, angiogenesis/angiostasis and Thr1/Thr2 development, with particular focus on regulating leukocyte trafficking.[66,71-73]

Chemokine Receptor	***Human Chemokine Ligand/s***	***Chemokine Receptor***	***Human Chemokine Ligand/s***
CXCR1	CXCL1, 6 & 8*	CCR3	CCL2, 5, 7, 8, 11*, 13, 15, 24*, 26* & 28.
CXCR2	CXCL1-8	CCR4	CCL17 & 22
CXCR3	CXCL9-11	CCR5	CCL3-5, 8, 11, 14 & 16
CXCR4	CXCL12[#]	CCR6	CCL20
CXCR5	CXCL13	CCR7	CCL19 & 21
CXCR6	CXCL16	CCR8	CCL1*, 4, 16 & 17
CXCR7	CXCL11 & 12[~]	CCR9	CCL25
CCR1	CCL3, 5, 7, 8, 13, 14, 15*, 16 & 23*	CCR10	CCL27 & 28
CCR2	CCL2*, 7, 8, 11, 13, 16	XCR1	XCL1 & 2
		CX3CR1	CX3CL1

Table 1. Summary of the known chemokine receptors and their human ligands. * Indicates the principal endogenous agonist/s. [#]Specfically; SDF-1α & SDF-1β, the active isomers of CXCL12. [~]Specifically; SDF-1α.

Chemokine receptors are based on and named after the chemokine class that bind to them, with ten human chemokine receptors being highly selective (K_d ~ 1 nM) for one main endogenous chemokine ligand (monogamous receptors): CXCR1, CXCR4, CXCR5, CXCR6, CCR6, CCR8, CCR9, CCR10, XCR1 and CX_3CR1. The other nine chemokine receptors are undiscriminating. It has become clearer that chemokines and their receptors can be usefully sub-classified into homeostatic leukocyte homing molecules (CXCR4, CXCR5, CCR7, CCR9) versus inflammatory/inducible molecules (CXCR1, CXCR2, CXCR3, CCR1-6, CX_3CR1).[74-76]

1.2.3 GPCRs

GPCRs, also known as 7-transmembrane (7TM) receptors, are part of a very large group of receptors which share a common protein structure. They interact with G-proteins and control signal transduction pathways in different ways which are involved in signalling a broad spectrum of biological processes such as peptide hormones, neurotransmitters, neuropeptides and odorants. They play an important role in physiological regulation and their malfunction can result in many diseases, so it comes as no surprise that they are a major class of drug target and are incredibly important to the pharmaceutical industry. Indeed, it is thought that GPCRs are targets for more than 50% of the current therapeutic agents, and their importance cannot be emphasised more than the awarding of the 2012 Nobel Prize in Chemistry "for studies of G-protein-coupled receptors".[77]

GPCRs can exist as either an active or inactive form. The GPCR is activated by an external signal in the form of a ligand or other signal mediator interacting with a cavity of the transmembrane domain at the *N*-terminus, whilst the *C*-terminus is bound to G-proteins within the cell. Upon activation of GPCRs, GPCRs associate with distinct classes of heterotrimeric G-proteins composed of three subunits: the α-subunit that has the guanine-nucleotide binding site and GTPase activity, and the β- and γ-subunits that form a tightly bound dimer.[78-81] Activated GPCRs promote the release of guanosine diphosphate (GDP) from the inactive α-subunits of G proteins and the binding of guanosine triphosphate (GTP), which then leads to the formation of free α-GTP and βγ-subunits that are able to interact with a diverse array of effector enzymes and ion channels (**Figure 6**). This change in activity is thought to be due to the terminal phosphate group which, in the GTP-bound form, stabilises the Gα protein.

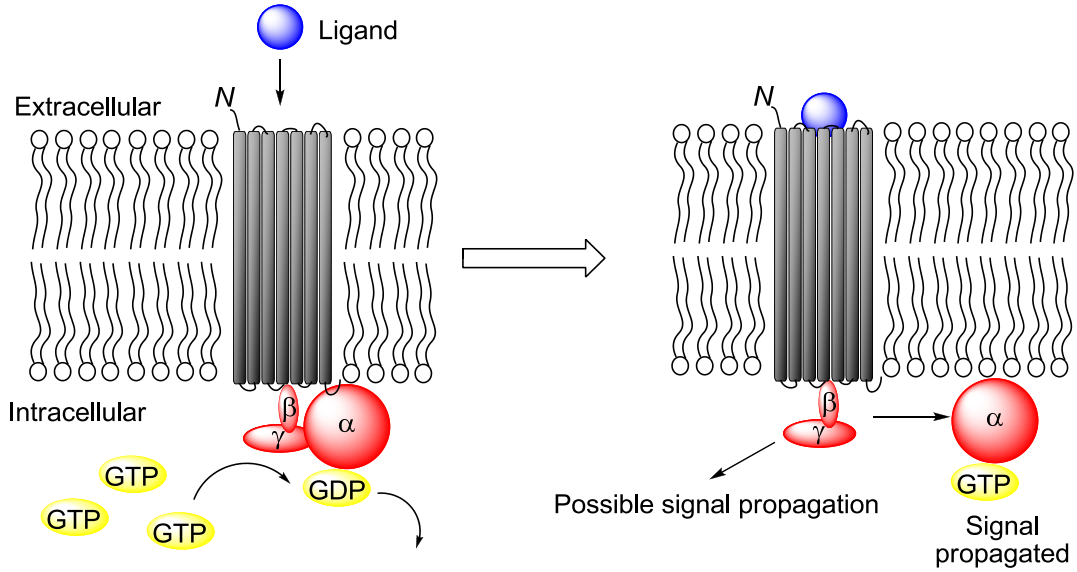


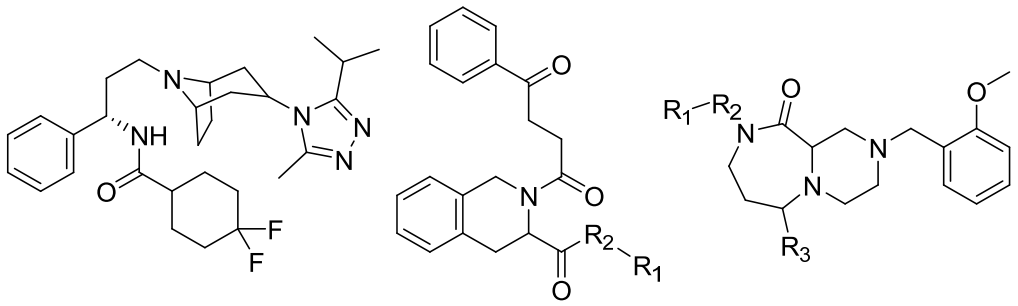
Figure 6. GPCR activation and mechanism through ligand binding. A ligand binds to GPCR inducing a conformational change which exchanges GDP with GTP at G-α. Free α-GTP and βγ subunits can then influence enzymes and cells.

Due to the success of small molecule inhibitors of GPCRs in the treatment of many diseases,[23,82] and the fact that chemokine receptors are GPCR expressed, small molecule inhibitors of chemokine receptors become an attractive therapeutic target, and one which is extensively researched with great interest to the pharmaceutical industry.

1.2.4 Chemokines as Pharmaceutical Targets

One problem in investigating the roles of chemokines and their possible role in the pathogenesis of a disease is the fact that chemokine receptors can bind to several different chemokines, and each chemokine can bind to several different receptors.[83] Each receptor-chemokine combination may direct a different inflammatory response and this response can be tailored by the body based on the type of injury or threat. There are two approaches for pharmaceutical targets: chemokine receptor antagonists, which target single chemokine/chemokine receptor combinations and chemokine inhibitors, which target a range of chemokine/chemokine receptor combinations. For the former, with the exception of selective CCR5 antagonists for HIV,[84] such as Celsentri (**1.20**)[85] and Fuzeon,[86]

the promise of obtaining new therapeutics related to chemokine receptors has not yet been realised.[87-88] Grainger *et al.* took the first step towards designing small molecule inhibitors of monocyte chemoattractant protein-1 (MCP-1), now known as CCL2, and testing these *in vitro*.[89-91] Importantly, once these inhibitors were identified *in vitro*, progress for anti-inflammatory activity *in vivo* leading to the controlling of the inflammatory response during many diseases could be realised. Recently published CXCR3 agonists include tetrahydroisoquinolines (**1.21**) and fused piperidinyl diazepanones (**1.22**),[92-93] but unfortunately of all the antagonists to date, none have been approved for the treatment of inflammatory and/or autoimmune diseases.[94]



1.20 **1.21** **1.22**

For the later class of inhibitors, Fox and colleagues have developed a novel form of anti-inflammatory chemokine inhibitor, broad-spectrum chemokine-inhibitors (BSCIs).

1.3 Broad Spectrum Chemokine Inhibitors (BSCIs)

1.3.1 Peptide 3 – The First BSCI

The first chemokine inhibitor, was derived from the human MCP-1, or CCL2, sequence (*vide supra*).[89] It is a 12-amino acid linear peptide corresponding to amino acids 51 to 62 of CCL2, with the sequence EICADPKQKWVQ (**Figure 7**).

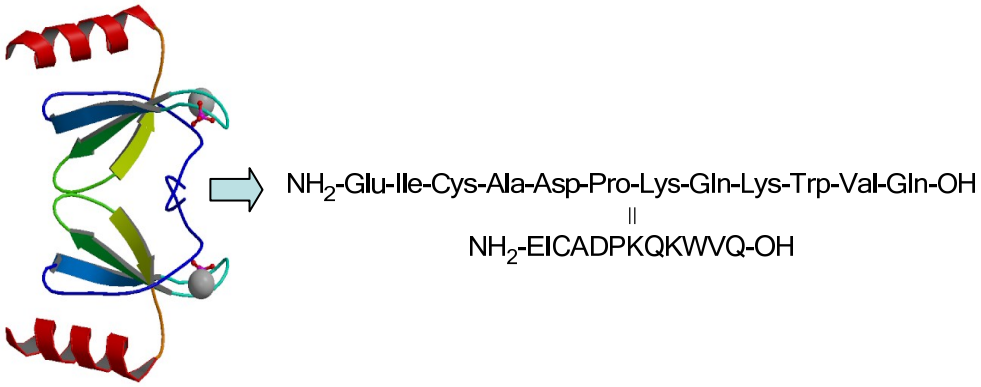


Figure 7. Amino acid sequence of the first broad spectrum chemokine inhibitor derived from CCL2, *Peptide 3*.

It was found that this amino acid sequence, termed *Peptide 3*, was a highly effective inhibitor for a wide range of chemokines *in vitro* in response to CC or CXC chemokine induced mononuclear-cell migration, with its ED_{50} being between 8 and 14 μM. It was also found that THP-1 cell migration, a leukemia cell line, was also inhibited, but the peptide has no effect on leukocyte migration induced by a range of other pro-inflammatory signals, thus it was dubbed the first example of a BSCI.[90-91] Subsequently, a number of studies on *Peptide 3* were carried out, in order to increase its potency and its inhibition *in vivo*.

1.3.2 NR58-3.14.3

A range of strategies have been used in the past to convert peptides with biological activity *in vitro* into agents with activity *in vivo*, including the design and synthesis of retro-inverse peptides in which *L*-amino acids are substituted with *D*-amino acids in the reverse sequence.[95] By utilising these strategies the first two amino acids of *Peptide 3* were removed and the amino acid sequence was reversed and replaced with *D*-amino acids. Cyclisation by adding a cysteine residue and oxidiation to give a di-sulfide bridge produced *NR58-3.14.3* (**Figure 8**) which was a thousand fold more active than *Peptide 3* and a potent inhibitor *in vivo*.

Interestingly, *NR58-3.14.3* inhibited inflammation in a number of disease models, such as atherosclerosis, ischemia, lung disease, surgical adhesions, endometriosis and pulmonary graft-versus-host disease, and is therefore a powerful anti-inflammatory agent *in vivo*, suppressing pro-inflammatory cytokine production and leucocyte recruitment while retaining the broad spectrum inhibitory activity of the parent peptide.[91]

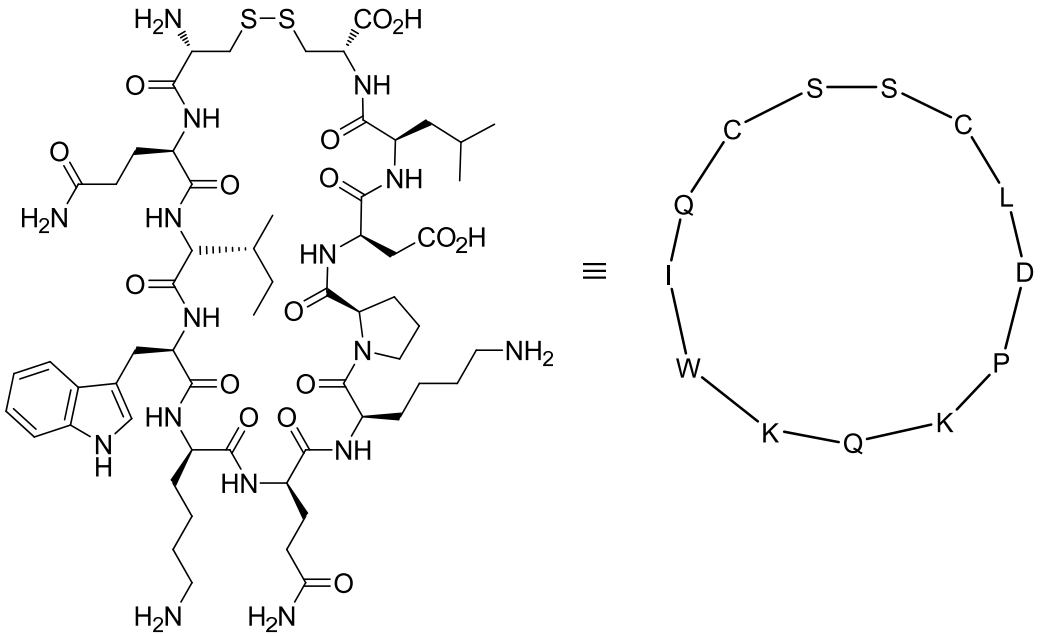


Figure 8. NR58-3.14.3, the reverse cyclised *D*-amino version of *Peptide 3*, with increased chemokine inhibition and *in vitro* activity.

Unfortunately there are limitations on the use of oligopeptides, both experimentally and therapeutically *in vivo*, and *Peptide 3* and *NR58-3.14.3* are not exempt from these, with both oligopeptides having poor oral bioavailability and short plasma half-lives.

1.3.3 SAR - The Critical Motif and Non-Peptide Analogues

In order to design a non-peptide BSCI mimetic that retained the broad specificity of the original peptides a structure-activity relationship (SAR) analysis was performed to identify the critical motifs required.

After much investigation it was found that a tryptophan (W), glutamine (Q) motif, **WχQ**, with a suitable spacer (dubbed χ here) was needed for BSCI activity (**Figure 9**). Results suggested a molecule with the presence of an aromatic group, or at least a bulky hydrophobic group, at an appropriate distance from a glutamine like primary amide was needed.

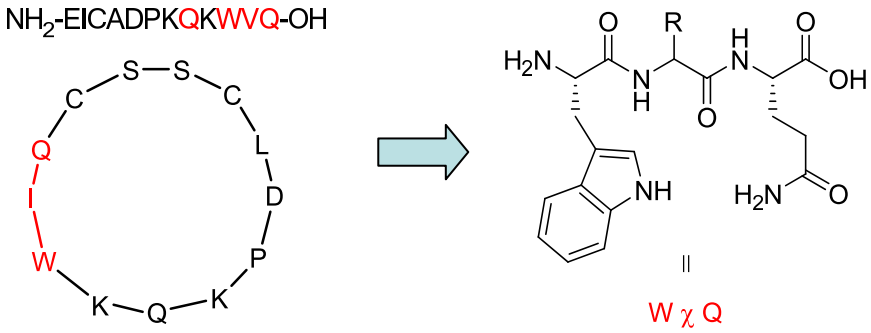
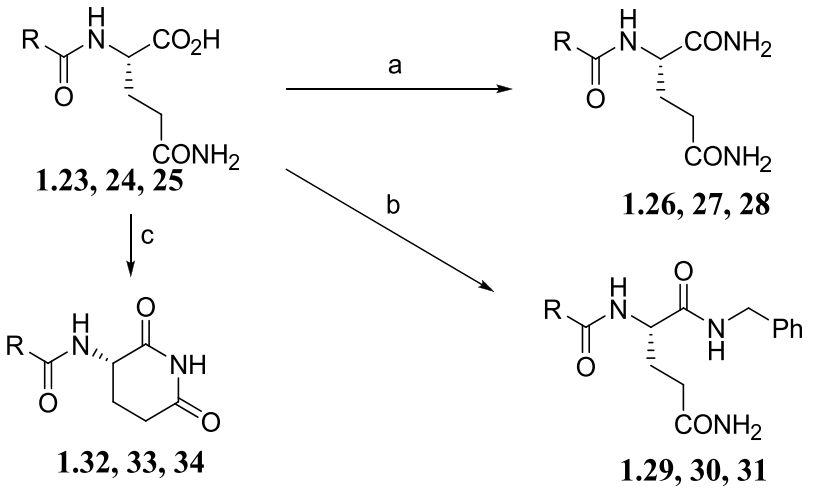


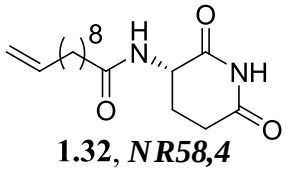
Figure 9. The critical motif in order to retain BSCI activity from oligopeptides *Peptide 3* and *NR58-3.14.3* was found to be tryptophan-spacer-glutamine.

With the critical motif of tryptophan-spacer-glutamine now established, the design and synthesis of non-peptide BSCIs could be realised and experiments were carried out using four glutamine mimetics; *N*-acylated products, *bis*-primary amides, benzylamides and acylaminoglutarimides. Combinations with three large hydrophobic groups gave twelve compounds for testing (**Scheme 1**). They were all synthesised using standard peptide coupling reagents and conditions.[96-97]



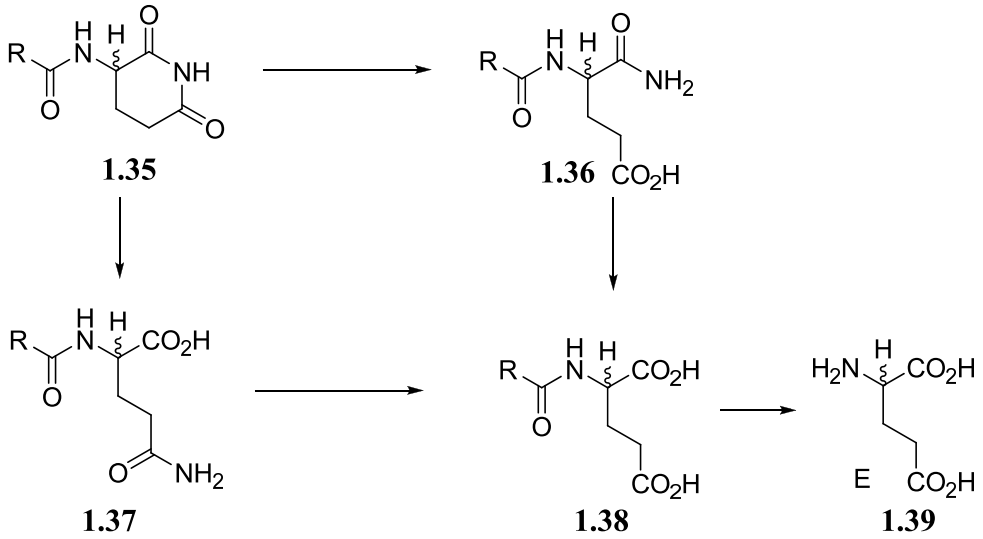
Scheme 1. Design and synthesis of non-peptide analogues of oligopeptides *Peptide 3* and *NR58-3.14.3*. (a) BOP, NEt_3, DMF, NH_3. (b) BOP, NEt_3, DMF, $PhCH_2NH_2$. (c) DCC, NHS, DMF, Δ. R = $(CH_2)_8CH{=}CH_2$ (1.23, 26, 29, 32). R = Ph (1.24, 27, 30, 33). R = ^tBuO (1.25, 28, 31, 34).

The best of this series of compounds was the (*S*)-*N*-undec-10-enoyl-3-aminogluarimide (**1.32**), dubbed *NR58,4* with an ED_{50} of 5 nM, even more potent than previously reported BSCIs.[71] At high dosages an anaesthetic effect was observed, with no toxic effects at high or low dosage. The cheaper synthesis of *NR58,4* meant it was a basis for further investigation into this class of drug *in vivo*.



1.32, ***NR58,4***

Surprisingly, although **1.32** is an effective anti-inflammatory agent in models of acute inflammation, it was apparent that it is much less effective than the parent oligomers, *Peptide 3* and *NR58-3.14.3*, in models of chronic inflammation. Pharmacokinetic studies were carried out to determine the fate of these molecules *in vivo* and it was found that imides of this type undergo rapid degradation *in vivo* as a result of enzymatic ring opening, producing isoglutamine (**1.36**), *N*α-acyl-glutamine (**1.37**) and *N*-acyl glutamic acid (**1.38**) metabolites (**Scheme 2**).[97]



Scheme 2. Possible degradation pathways of BSCIs in vivo.

1.3.3.1 Lactam BSCIs

In order to prevent this degradation but retain the BSCI activity, a series of 5 (-γ), 6 (-δ) and 7 (-ε) membered lactams (**Figure 10**) were synthesised and, although each lactam had a lower efficacy than its parent imide, the caprolactam (**1.43**) looked promising.

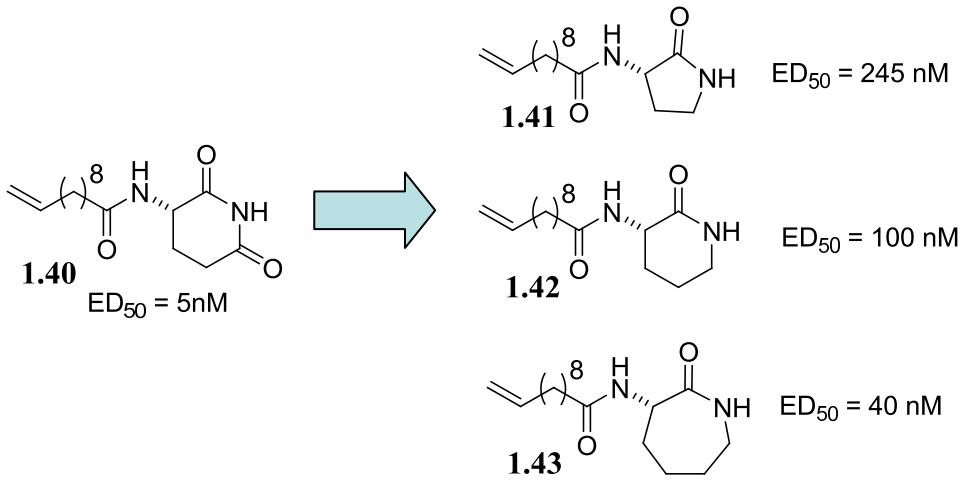
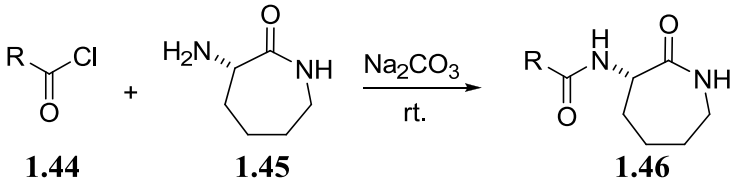


Figure 10. Lactams synthesised in order to resist degredation *in vivo*. The ED_{50}'s are shown for comparison.

Naturally, this led to an extensive investigation of the side chain of the caprolactam by altering the acyl side chain using simple acylation chemistry (**Scheme 3**) on (*S*)-3-aminoazepan-2-one (**1.45**), with interesting results.[98] The presence of a quaternary carbon at the α-position of the side chain dramatically

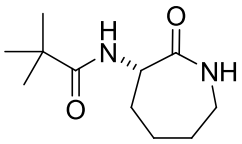
increased the potency of the BSCIs while shortening the long lipophilic side-chain increased their oral potency by over 1000-fold. It was also shown that, like the aminoglutarimides, the (*S*)-enantiomers of the lactams were more potent than the (*R*)-enantiomers.



1.44 **1.45** **1.46**

Scheme 3. Caprolactam side chain investigation. Acylation chemistry used to identify the best side chain for BSCI activity.

One of the most potent and successful BSCIs synthesised by the Fox group, (*S*)-3-(2',2'-dimethyl-propionyl)amino-caprolactam (**1.47**), contains a caprolactam and a hydrophobic tertiary butyl group, with an ED_{50} of 40 pM (or 0.04 nM). Its ease of synthesis combined with its outstanding potency means that similar types of molecules are attractive targets for the pharmaceutical industry. Indeed, a compound similar to this, FX125L, is currently undergoing clinical trials as a powerful anti-inflammatory drug, and has passed phase I of clinical trials.[99-100]



1.47

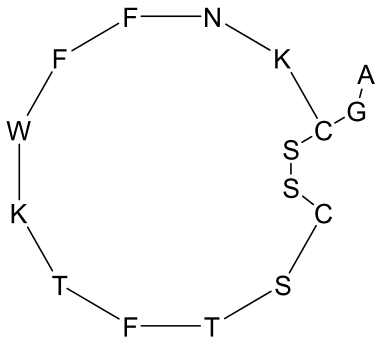
ED_{50} = 40pM

Despite being small and simple, obviously these types of molecules display complex pharmacology with further information regarding their mode of action *in vivo* needed. The original peptide BSCIs were designed to be chemokine receptor ligands, but it seemed more likely that BSCIs targeted a component of the chemokine signalling pathway associated with the migratory response.[90] Indeed it has since been found, through screening a large number of receptors, that it is in fact through the human type 2 somatostatin receptor (SSTR2), or one which is

closely related, where the inhibition of chemokine-induced leukocyte migration occurs.[101-103]

1.4 Somatostatin

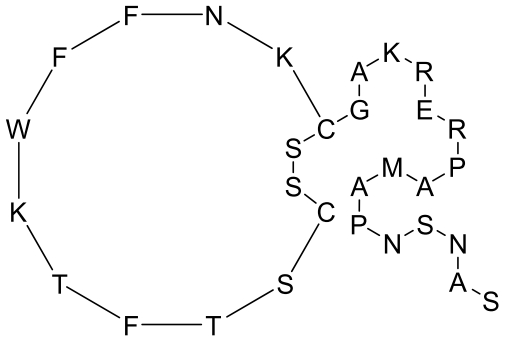
Somatostatin (SST, (**1.48**)), originally identified by Krulich and co workers,[104] is a peptide hormone with multiple physiological functions including inhibition of secretion of growth hormone (GH), glucagon, insulin, gastrin, and other hormones secreted by the pituitary and gastrointestinal tract. In humans SST, also known as a growth hormone-inhibiting hormone (GHIH) or somatotropin release-inhibiting factor (SRIF), is distributed throughout the endocrine system and was first located in the hypothalamus by Pelletier and co-workers.[105] It has also been implicated in affecting neurotransmission in the central nervous system as well as cell proliferation and is therefore regarded as a multi-functional peptide hormone.[106-109]



1.48

The structure of SST, first deduced by the nobel laureate Roger Guillemin[110] and co-workers, is a cyclic tetradecapeptide having the primary structure NH_2-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH with a disulphide bond between the cysteine residues, confirmed by using solid-phase peptide synthesis.

SST is synthesised as two active forms: the predominant, but functionally less active SST molecule consisting of 14 amino acids known as SST-14 (**1.48**) with a disulfide bond linking the cysteine residues at positions 3 and 14, and a larger more potent molecular form, SST-28 (**1.49**), which is a congener of SST-14 extended at the amino terminal.



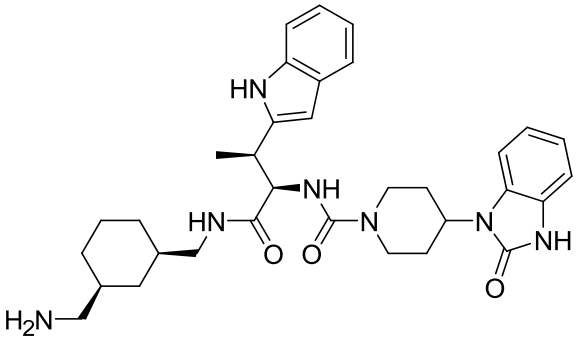
1.49

1.4.1 Somatostatin Receptors and SSTR2

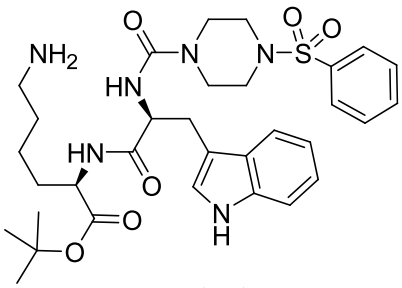
There are 5 known receptors of somatostatin, SSTR1 through to 5, with 6 separate receptor subtypes (SSTR2 being split into types A and B), and like chemokine receptors they too are all GPCRs.[106,111] They are expressed throughout the body in several different tissues and cell types, in varying numbers and combinations. SSTRs interact with several types of Gα, β and γ proteins and have also been shown to interact directly with structural cell proteins through their C-terminal domains.

SSTR2 is responsible for the inhibition of glucagon and GH, and it is now apparent that BSCIs act through the somatostatin type 2, or a closely related, receptor. A group at Merck synthesised the first potent non-peptide agonist which selectively bound to the SSTR2 receptor.[108] An integrated approach of combinatorial chemistry and high-throughput receptor-binding techniques was

used to rapidly identify subtype selective compounds, with compound L-779,976 (**1.50**) giving the best results. The first small molecule SSTR2 antagonists (**1.51**) were synthesised by Pfizer in the hope of up-regulating GH in farm animals.[112-113]



1.50



1.51

1.4.2 Somatostatin, BSCIs and Inflammation

The current mechanistic thought process is that agonism by somatostatin inhibits growth hormone and not chemokine inhibitiors, but agonism by the BSCI class of molecules results in inhibition of cell migration, or chemotaxis. The mechanism is thought to be similar to that shown in **Figure 11**.[102]

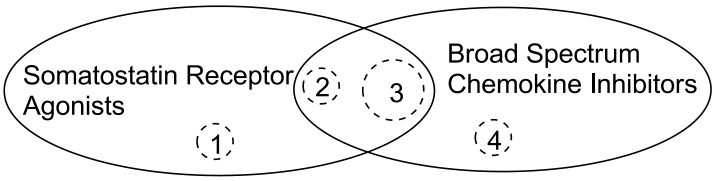
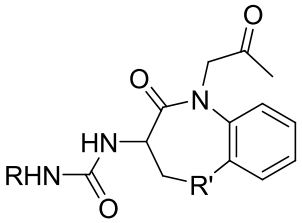


Figure 11. Diagramatic representation of the current proposed mechanism of sstr2 ligands and BSCIs. 1 - Classical agonist lacking BSCI activity, 2 - Powerful agonists which exert a degree of BSCI activity, 3 - BSCIs acting through SSTR2, or a closely related receptor, 4 - BSCIs acting by other mechanisms at somatostatin receptors.

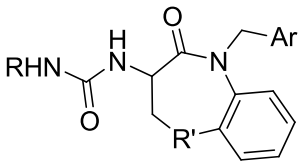
1.5 Research Hypothesis

A number of benzothiazepinone GPCR ligands are already known in literature, most notably compounds **1.52** and **1.53**.[114-116]



R' = CH_2, O, S

1.52



R' = CH_2, O, S

1.53

With the knowledge of GPCR ligands and our experience in the field of BSCIs, hopefully we can exploit the known therapeutic pathway both in acute and chronic inflammation and build new GPCR ligands with increased functionality and structural diversity. In the process we can investigate further the true biological mechanism, devise new specialised libraries and aid in drug discovery. Importantly the new compounds synthesised will differ from known GPCR ligands because they will not have the benzene moiety a carbamide moiety or any substitution at the *N*-4 position. The chemistry used to synthesise these new ligands could simultaneously be exploited to synthesise further novel lactams or heterocycles which may have important medicinal properties.

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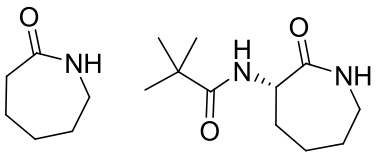
Chapter 2 – γ-Thialactams

2.1 Introduction

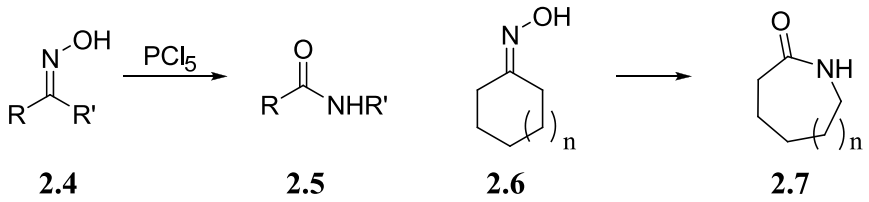
Caprolactam (**2.1**), a derivative of azepine, is without doubt one of the most useful and important lactams.[117] It has been used extensively as a precursor in the manufacture of nylon 6, with quantities in excess of 2 billion kilograms being produced annually.[118-122] Simple *C*-substitiuted caprolactams possess significant central nervous system (CNS) activity[123] while other derivatives have useful analgesic effects[124] and have found use as antitussives, mydriatics, antispasmodics and oral hypoglycaemics.[125,126] Noteworthy are the broad spectrum inhibitors of chemokines, previously discussed, with structures similar to **2.2**. The synthesis of *C*- substituted caprolactams such as compound **2.3** would give valuable insights into the mechanistic and pharmacological outcome of this class of drug. The synthesis of these molecules might prove difficult as only a small number of general methods exist for the stereoselective preparation of such systems.



2.1 **2.2** **2.3**

2.1.1 Routes to C-Substituted Lactams

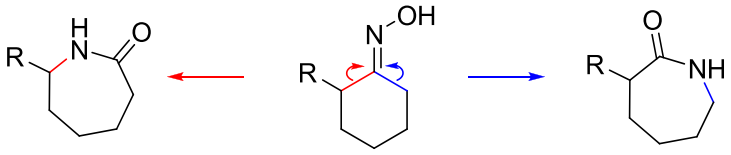
The Beckmann rearrangement (**Scheme 4**), first reported by Beckmann in 1886, is the acid mediated isomerisation of oximes (**2.4**) to amides (**2.5**).[127,128] Lactams are obtained from the rearrangement of alicyclic oximes (**2.6**) and are unproblematic for simple substrates and for cases where n = 1, 2 and 3. The Beckmann rearrangement is a highly efficient and versatile process in the synthesis of lactams.



2.4 **2.5** **2.6** **2.7**

Scheme 4. The Beckmann rearrangement of oximes to amides (left) and alicyclic oximes to lactams (right).

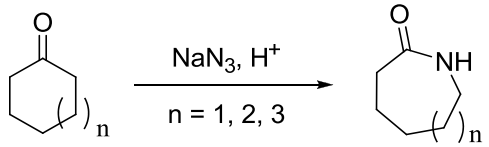
Unfortunately problems arise in cases of unsymmetrical oximes (**2.8**) where usually a mixture of products is obtained *via* two possible pathways (**Scheme 5**).[129] Although *anti*-rearrangement is favoured with the most substituted carbon migrating, both pathways can occur.



2.9 **2.8** **2.10**

Scheme 5 The two possible pathways of the Beckmann rearrangement with the *anti*-rearrangment (red arrow) being favoured.

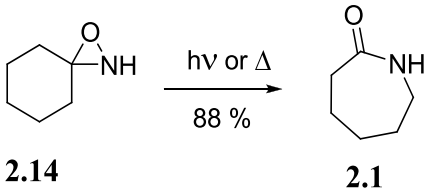
Similarly the Schmidt reaction[130,131] of alicyclic ketones (**2.11**) is an efficient way of synthesising lactams (**Scheme 6**) but again has the problem of giving a mixture of products with unsymmetrical ketones.



2.11 **2.1, 2.12-2.13**

Scheme 6. The Schmidt reaction (or rearrangement)

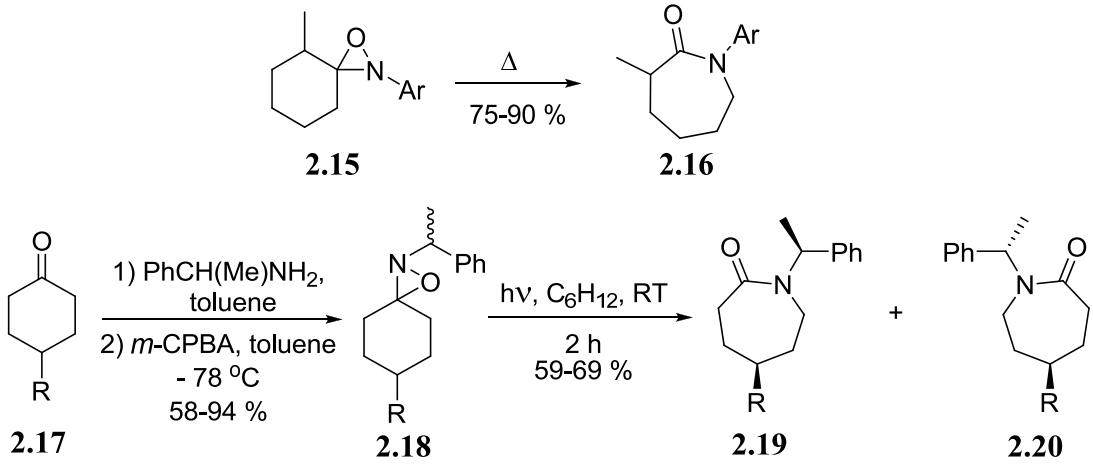
The limited selectivity and lack of flexibility in the ring expansion has created the need for a more flexible process. A general route to caprolactams is the intramolecular cyclisation of ε-aminohexanoic acids,[132] but yields for **2.1** are low. Thermal or photochemical induced ring expansions of oxaziridines to azepan-2-ones are possible,[133,126] for example flash pyrolysis of oxaziridine (**2.14**) affords the corresponding caprolactam (**Scheme 7**).



Scheme 7. Caprolactam *via* flash pyrolysis

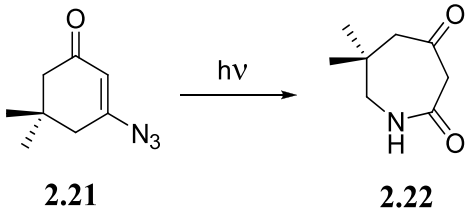
Surprisingly, *only a few general methods are known for the preparation of C-substituted azepan-2-ones*.[125] These include:

- Photochemical rearrangement of oxaziridines (such as **2.15** and **2.18**) developed by Aubé[134-137] after pioneering work by Lattes[138] and co-workers.



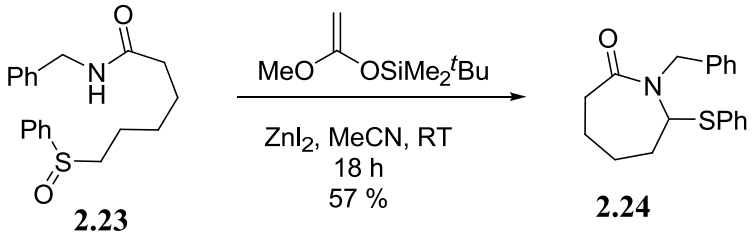
Scheme 8. Rearrangement of oxaziridines to form lactams.

- Photoinduced ring expansion of azidocyclohexenone (**2.21**) described by Sato.[139]



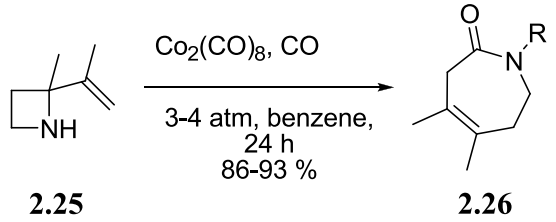
Scheme 9. Ring expansion to form lactams.

- Cyclisation of a novel sila-Pummerer rearrangement of ω-amidosulfoxides (**2.23**) by Kita and co-workers.[140,141]



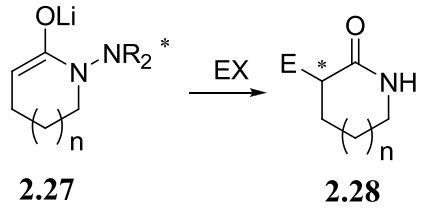
Scheme 10. Cyclisation of sulfoxides to form lactams.

- Cobalt-mediated carbonylation of 2-vinylazetidines (**2.25**) developed by Alper.[142]



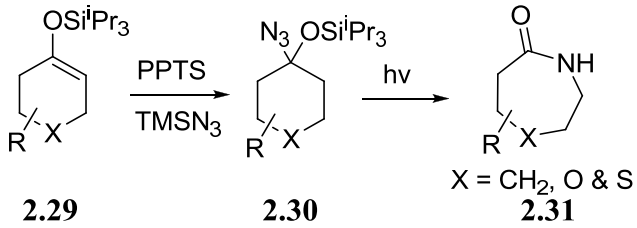
Scheme 11. Carbonylation to form lactams.

- α-Alkylation of chiral *N*-dialkylamino derivatives (**2.27**) developed by Enders.[143]



Scheme 12. Alkylation of lithium derivatives to form lactams.

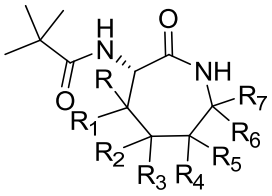
- Photoinduced Schmidt rearrangement from (triisopropylsilyl)-azidohydrin derivatives (**2.29**) reported by Evans.[144]



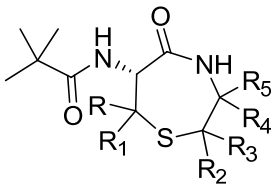
Scheme 13. Schmidt rearrangement of azidohydrin derivatives to form lactams.

Although the synthesis of *C*-substituted azepan-2-ones (**2.3**) would be desirable to further our research for drug design by optimising the target interactions of our

lead compound, the inherent difficulty in their synthesis, lack of efficiency and versatility in their preparation call for an alternative. We envisaged the 1,4-thiazepan-5-one derivatives (**2.32**) as a good alternative, not merely because of their relative ease of synthesis and robustness, but also because this moiety has been seen and synthesised within a number of medicinally important compounds. It is also known that the inclusion of a sulfur atom within certain lactam rings has little impact on the biological effect of the related lactam.



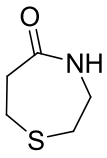
2.3



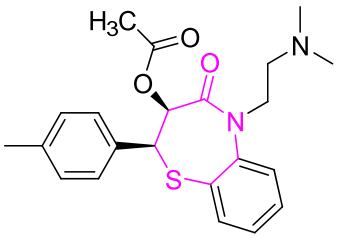
2.32

2.1.2 1,4-Thiazepan-5-one Moiety

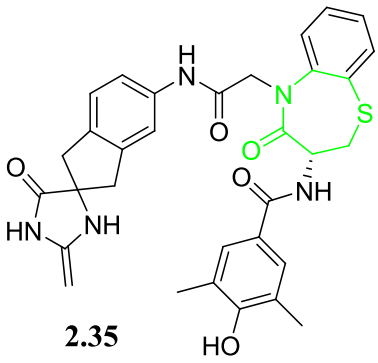
The 1,4-thiazepan-5-one moiety (**2.33**) has been the subject of intense interest within chemical and pharmacological research since the discovery that some members of the group were angiotensin converting enzyme (ACE) inhibitors.[145] It can be seen in the drug diltiazem (**2.34**),[146-147] used for angina and heart problems, and a potent calcitonin gene-related peptide (CGRP) receptor antagonist (**2.35**),[148] as well as in numerous ACE (**2.36**) and interleukin-1 converting enzyme (ICE) inhibitors (**2.37**).[145,149-150]



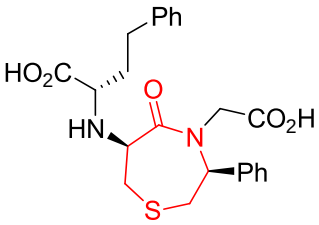
2.33



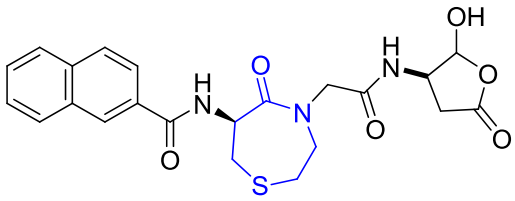
2.34



2.35



2.36



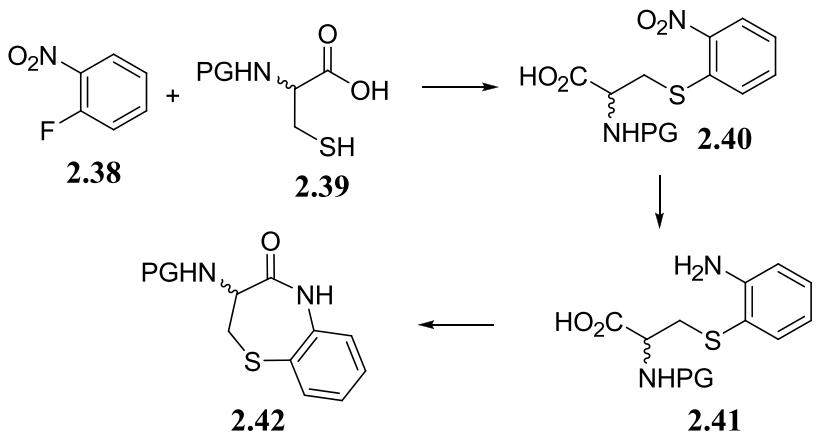
2.37

The 1,4-thiazepan-5-one moiety is contained within the benzothiazepinone moiety which has frequently been employed as a scaffold for the development of peptidomimetics with their preparation generally being more straightforward.[151] The benzothiazepinone derivatives also possess various biological activities. Although we are not interested in the synthesis of benzothiazepinones it is apparent that the chemistry used in their syntheses might be applicable to the synthesis of our lactams.

2.1.2.1 Synthesis of Thiazepan-5-one Moiety

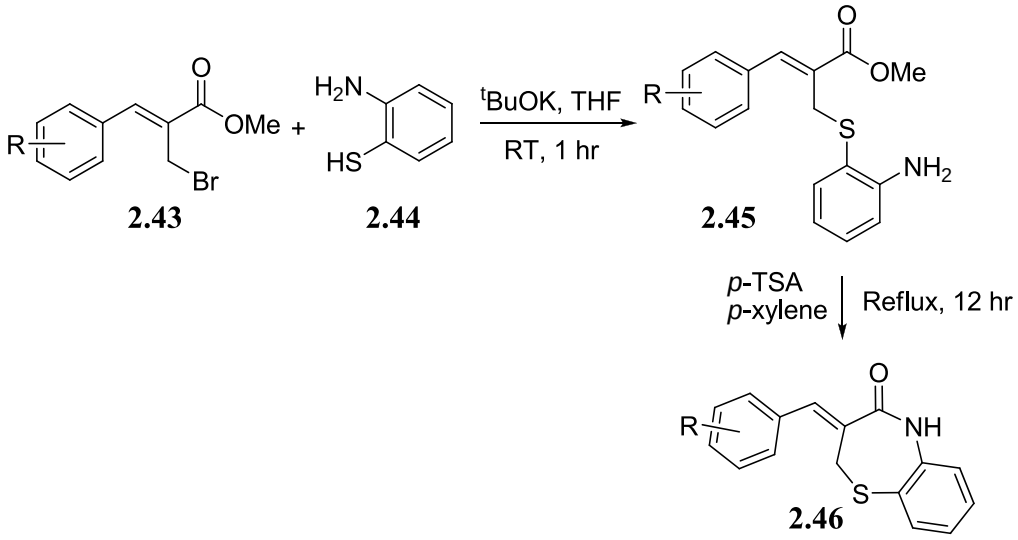
Synthetically, these structures have been made in a number of different ways. These include:

- Aromatic nucleophilic substitution of *o*-fluoronitrobenzene (**2.38**) with a protected cysteine derivative (**2.39**) followed by reduction of the nitro compound and ring closure.[152-154]



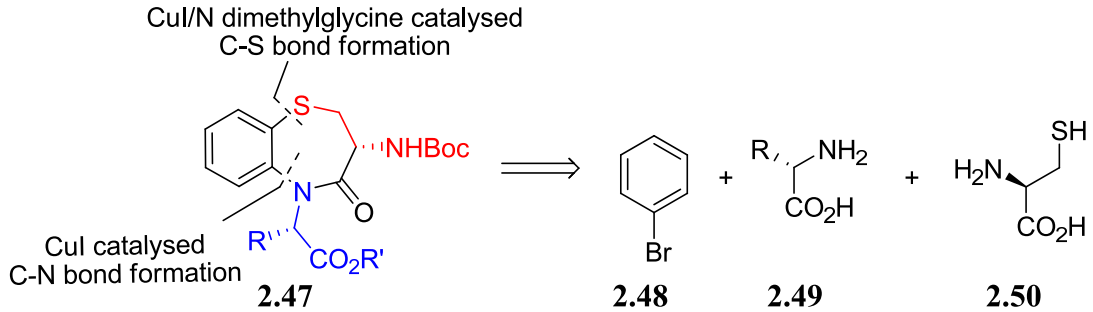
Scheme 14. Thiazepan-5-one moiety *via* aromatic nucleophilic substitution.

- Utilising bromo compounds derived from Baylis–Hillman adducts (**2.43**) involving selective *S*-alkylation followed by lactam formation.[155-157]



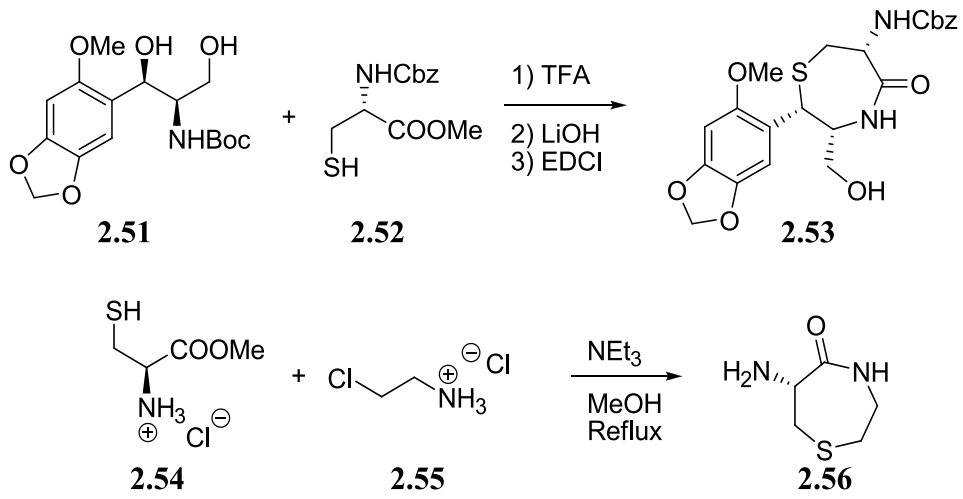
Scheme 15. Thiazepan-5-one moiety *via S*-alkylation and ring closure.

- CuI catalysed coupling.[150]



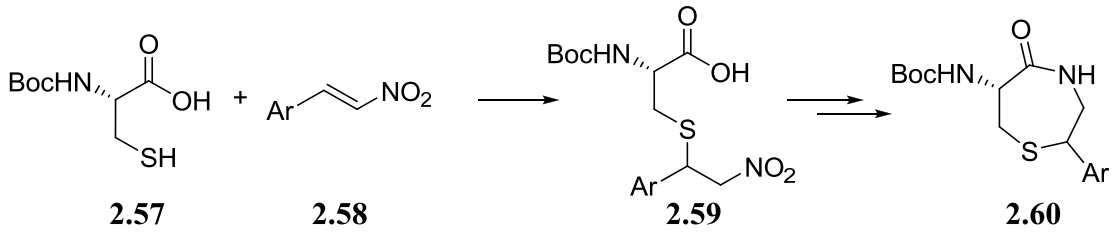
Scheme 16. Thiazepan-5-one moiety *via* CuI catalysed coupling.

- Condensation of an amino alcohol (**2.51**) or halo-ethylamine (**2.55**) with a suitably protected cysteine residue ((**2.52**) or (**2.54**)).[149,158-160]



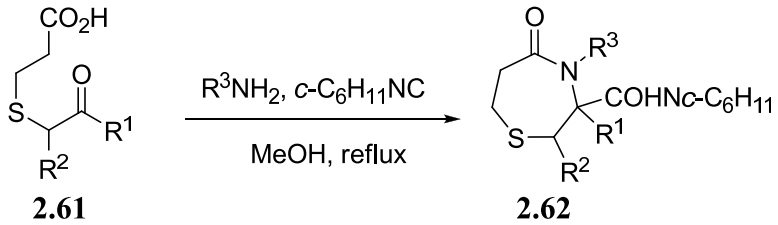
Scheme 17. Thiazepan-5-one moiety *via* condensation of a protected cysteine residue.

- Michael addition of a β-nitro olefin (**2.58**) with a suitably protected cysteine residue.[145,161]



Scheme 18. Thiazepan-5-one moiety *via* Michael addition reactions.

- Intramolecular Ugi condensations.[162-163]



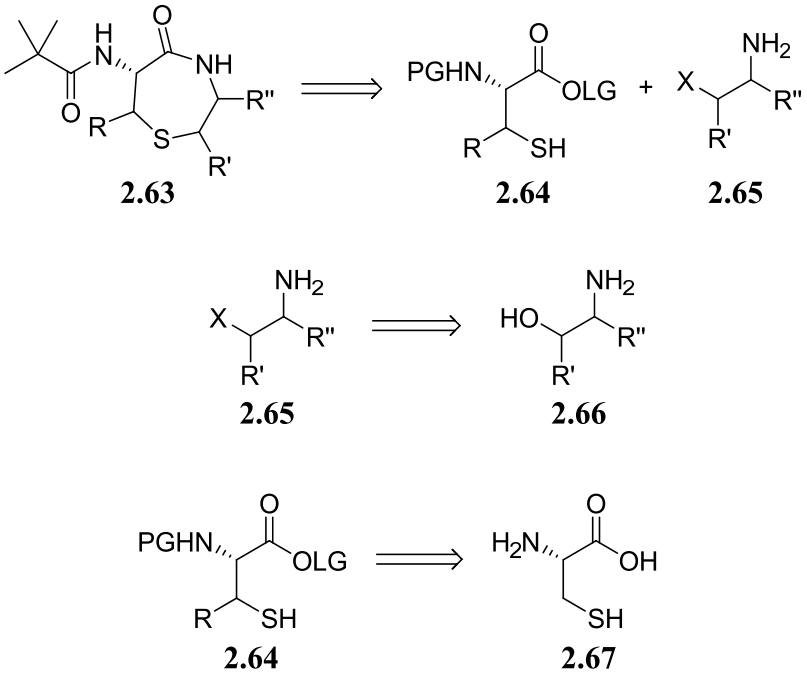
Scheme 19. Thiazepan-5-one moiety *via* Ugi condensations.

Many of these synthetic approaches to the thiazepan-5-one moiety are clearly related to the structures which we wish to synthesise. In all cases, the synthetic method is either limited in scope or versatility for our purposes, has substitution at

the *N*-4 position of the lactam, requires severe reaction conditions, is multistep or utilises chemistry which takes advantage of a benzene group, giving the undesired benzothiazepinone moeity.

2.1.3 Synthetic Strategy

The synthetic strategy usually employed in synthesising the 1,4-thiazepan-5-one moiety within the literature is the coupling of a protected cysteine derivative with a suitable amine derivative and cyclisation to form the lactam. Therefore for our purposes we proposed substituted amine derivatives that contains a β-leaving group (**2.65**), derived from a β-hydroxyamine (**2.66**), and a suitably protected substituted thiol derivative containing a leaving group (**2.64**), derived from cysteine (**2.67**) as shown in **Scheme 20**.



Scheme 20. Synthetic strategy to the thialactams

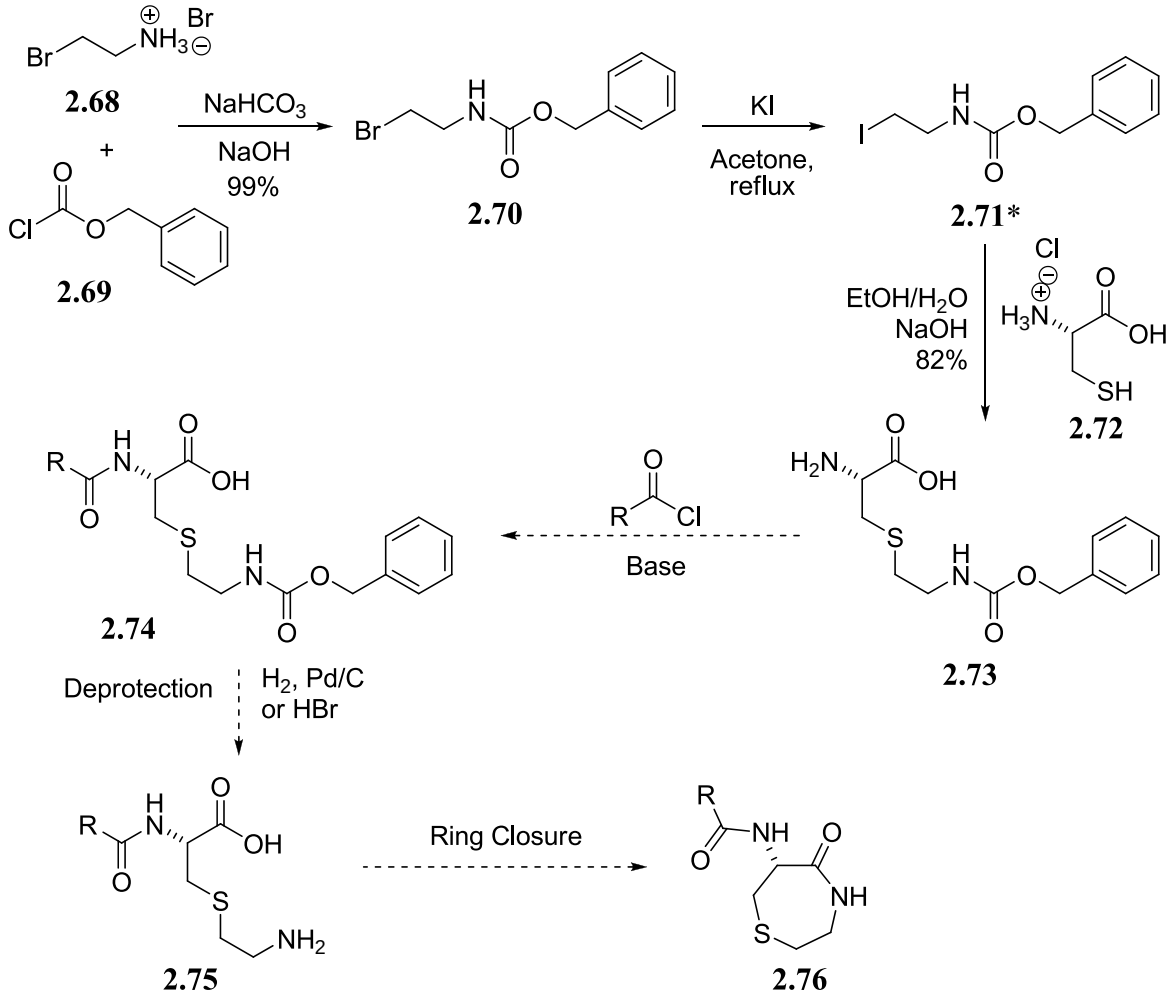
In order to test the viability of this strategy, and the project, firstly the simple 1,4-thiazepan-5-one would be synthesised ((**2.63**):R, R', R'' = H) for comparison with the analogus non-sulfur containing caprolactam (**2.3**) previously synthesised. If inserting sulfur into the ring has little to no effect on the molecules' properties or mode of action then the same synthesis could be used, depending on its robustness, and a library of substituted 1,4-thiazepan-5-ones realised. This could then in turn be used to build a structure activity relationship and discover which parts of the molecule are important for biological activity and whether *C*-substitiution helps the lead compound (**2.3**).

2.2 Lindley/Ahmed Methods

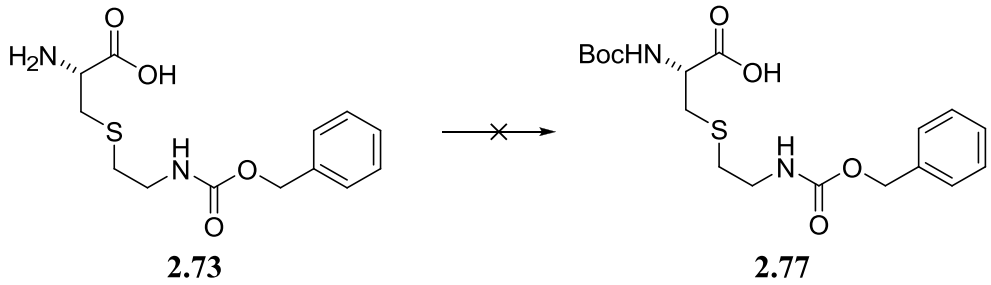
As eluded to, our original thought process into the synthesis of 1,4-thiazepan-5-ones was the coupling of cysteine with a suitably protected amine, acylation and ring closure. Lindley had previously published a paper[164] in 1959 on the synthesis of *S*-benzyloxycarbonylaminoethyl-L-cysteine (**2.73**) so our first attempt was to repeat this procedure and attempt a continuation to the thialactam (**Scheme 21**).

Unfortunately this original strategy posed a number of problems. Protection of 2-bromoethylamine hydrobromide (**2.68**) with benzyloxycarbonyl chloride (CbzCl, **2.69**) to produce the desired protected bromoethylamine (**2.70**) is straightforward, as is the Finkelstein reaction to the corresponding iodo-compound (**2.71**). The coupling of this iodo-compound to L-cysteine is where problems arose, with all attempts at the coupling failing. In every case a white solid was recovered from the coupling reactions but identification, purification and characterisation of such compounds proved difficult due to their extreme lack of solubility in any solvent. To try and resolve this problem slightly basic deuterated water was employed but even then the compounds were hard to characterise. Acylations on the

uncharactarisable compound, as well as attempting an *N-tert*-butoxycarbonyl (Boc) protection (**Scheme 22**), did not furnish the desired products, **2.74** and **2.77** respectively.

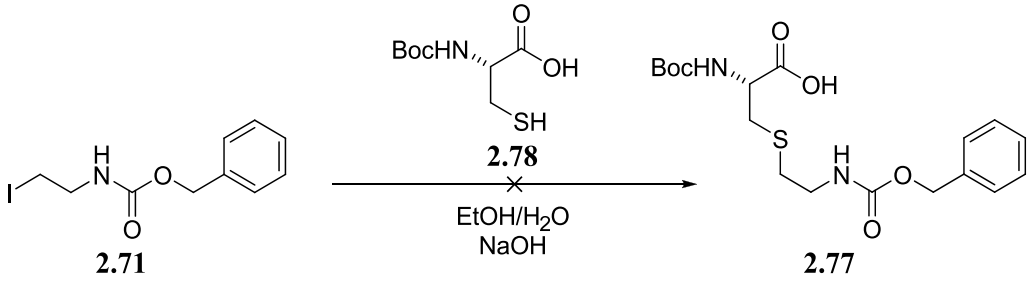


Scheme 21. First attempted synthesis of thialactam derivative *via* Lindley method. *Compound not purified and used directly.



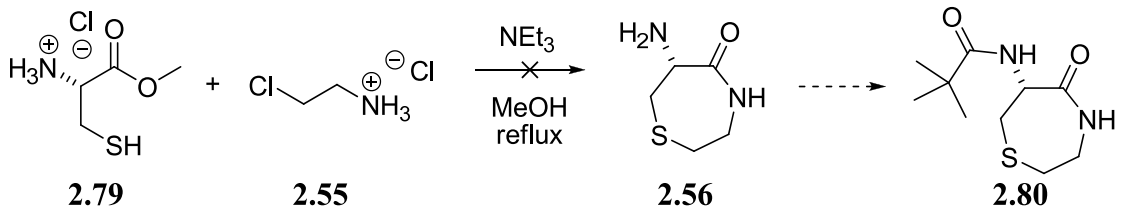
Scheme 22. Attempted Boc protections on thialysine derivative.

Attempts were also made to Boc-protect the cysteine before coupling (**Scheme 23**), which proved more difficult than first thought. Again characterising these proved difficult and it was unclear whether or not the reaction proceeded in the first instance.



Scheme 23. Attempted Coupling of a Boc-protected cysteine residue with protected ethylamine derivative.

Coupling reactions of the cysteine hydrochloride (**2.72**) directly with the protected bromo-ethylamine (**2.70**) to form the *S*-benzyloxycarbonylaminoethyl-L-cysteine (**2.73**), instead of performing the Finklestein and coupling, were carried out and again gave inconclusive results. At this early stage in the project it was decided a different strategy was needed for the synthesis of the thiazepan moiety. Firstly the synthesis of the simplest thiazepan-5-one (**2.56**) was attempted using a strategy published by Ahmed (**Scheme 24**) in 1984.[160]

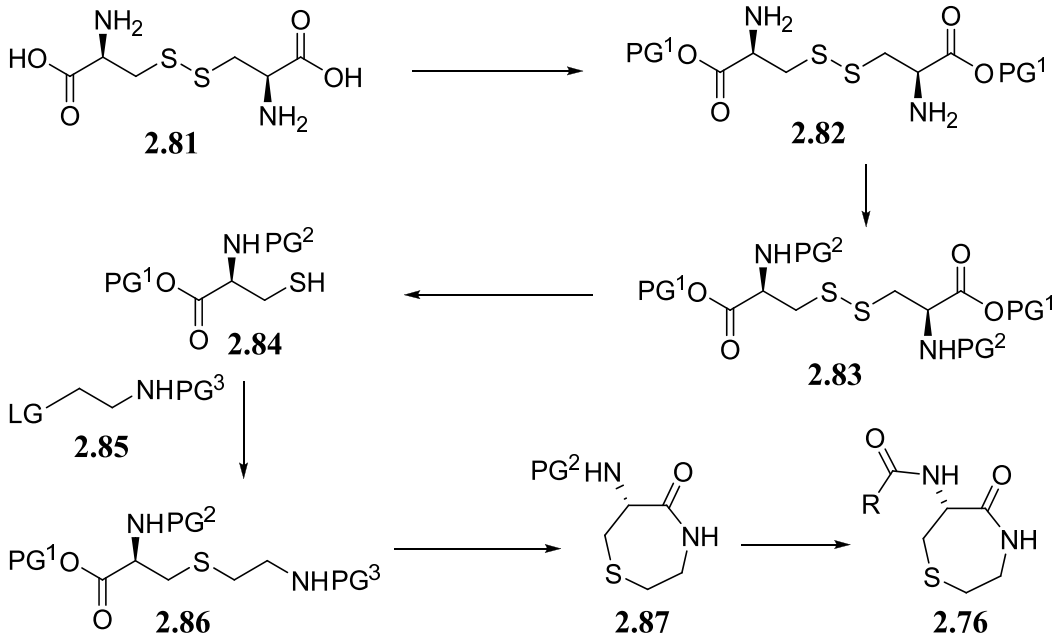


Scheme 24. Attempted Ahmed synthesis of thialactam

Unfortunately we could not reproduce the same results as the original paper; the reaction simply did not work for us. These first attempts were deemed unacceptable and an alternative strategy was needed.

2. 3 Modular Approach to Thialactams

Due to the lack of success *via* the Lindley and Ahmed methods, and a wealth of literature on lanthionine building blocks,[165-170] a modular approach to the synthesis of 1,4-thiazepin-5-one derivatives was the next logical step (**Scheme 25**). This approach involved five key elements: the protection of cystine (**2.81**) (the dimer of cysteine), its reduction, coupling with a suitable protected amine, ring closure to form the caprolactam (**2.87**) and finally deprotection and acylation of the head group. The similarity of this method to that of the Lindley and Ahmed methods are clear, with the exception that all reactive functional groups are now protected. Importantly, using the correct protecting group and leaving group chemistry was key to the synthesis of the final product, and also for important intermediates that could be used for further chemistry. For instance, the thialysine building block (**2.86**) could easily be utilised to synthesise somatostatin ligands.



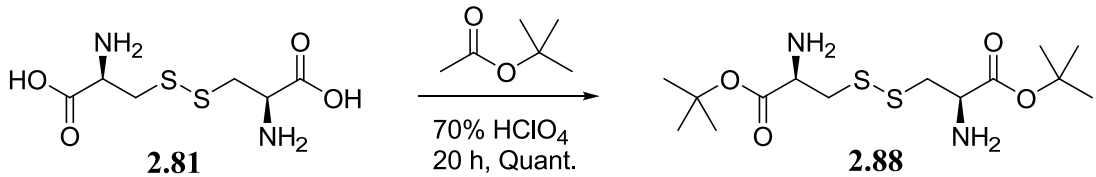
Scheme 25. Modular approach to the synthesis of the thialactams

With this in mind, we realised that the amine protecting group on the cysteine derivative (PG^2) would have to withstand amine and carboxylic acid deprotection conditions in order to generate the desired cyclised product (**2.87**) but also have the capability of being selectively labile itself for the useful thialysine building

block (**2.86**). With the wealth of literature and our experience in using carbobenzyloxy (Cbz), *tert*-butyloxycarbonyl (Boc) and 9-fluorenylmethyloxycarbonyl (Fmoc) protecting groups, we decided a combination of these would allow us to generate a robust thialysine derivative. The Boc protecting group is unreactive to most bases and nucleophiles, allowing for orthogonal Fmoc or Cbz protection, ideal for our scenario. We therefore envisaged the cystine (**2.81**) to be Fmoc or Cbz protected with the nucleophilic coupling of a Boc protected amine derivative (**2.85**). *tert*-Butyl (^{t}Bu) ester, a protecting group for carboxylic acids which is acid labile, would also allow the possibility of a double deprotection during the Boc deprotection reaction. Importantly the Fmoc or Cbz protecting groups could be deprotected selectively at either the thialysine (**2.86**) or lactam (**2.87**) stages.

2.3.1 Cystine Protection

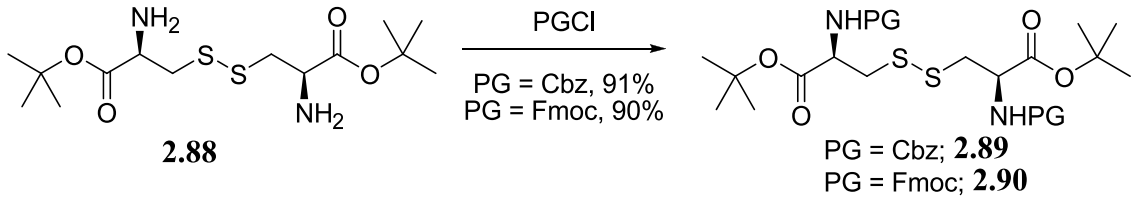
The initial reaction was the ester formation (or acid protection) of cystine derivative (**2.81**) which was achieved in quantitative yield using *tert*-butyl acetate and perchloric acid (**Scheme 26**) according to the method of Amaral.[171] This reaction was very straightforward with scales of 10 g of cystine easily converted to the product (**2.88**), although great care must be employed when using the extremely corrosive and explosive perchloric acid.



Scheme 26. Acid protection of cystine using ^{t}BuOAc & $HClO_4$.

Amine protection was achieved by using either fluorenylmethyloxycarbonyl chloride (FmocCl) or CbzCl (**Scheme 27**).[172-173] A bi-phasic reaction with aqueous $NaHCO_3$ and chloroform was the preferred method, giving higher and reproducible yields as originally the Fmoc protecting group was added using *N*-

methylmorpholine (NMM) in THF. Purification of a large quantity of the Fmoc material (**2.90**) posed problems as it was found that it decomposed during column chromatography. Recrystallisation from CH_2Cl_2:Methanol (1:5) afforded the product, but the yield was significantly reduced to 43%. After further investigation and continuation of the synthesis, Cbz was used exclusively as the amine protecting group.

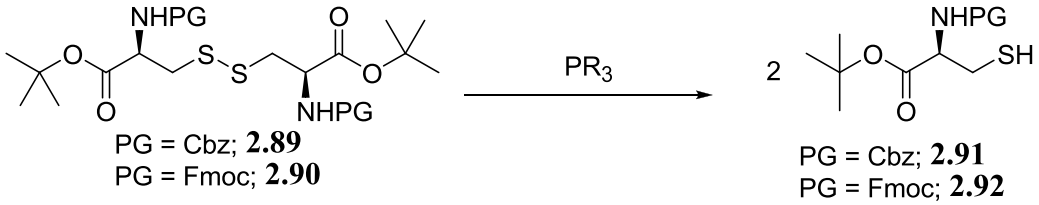


2.88

Scheme 27. Amine protection of protected cystine, the complete protection of cystine.

2.3.2 Reduction of Protected L-Cystine – The Use of Phosphines

The reduction of suitably protected L-cystine using phosphines was achieved *via* two methods, either using triphenylphosphine (PPh_3) or tributylphosphine (PBu_3), (**Scheme 28**).

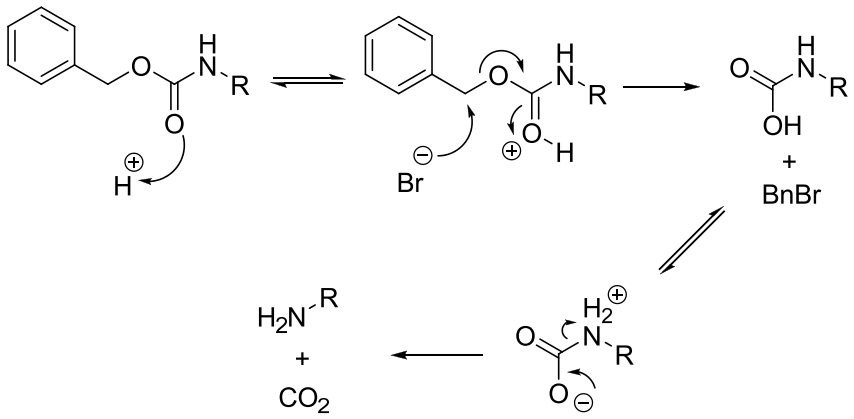


R	*Additives*	*Solvent*	*PG*	*Yield (%)*
2.91	PPh_3, ME	THF:H_2O (1:1)	Cbz	71
	PBu_3	THF:H_2O (10:1)	Cbz	99
2.92	PPh_3, ME	THF:H_2O (1:1)	Fmoc	53
	PBu_3	THF:H_2O (10:1)	Fmoc	< 10

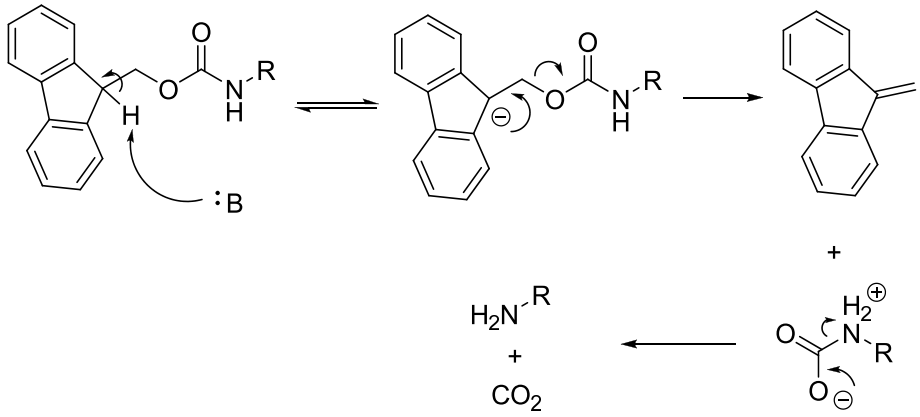
Scheme 28. Formation of protected cysteine; the reduction of protected cystine.

PPh_3 and 2-mercaptoethanol (ME) were used in THF and water, while PBu_3 was used in only THF and a little water. Reduction of Cbz protected cystine (**2.89**) was achieved in good and comparable yields for both PPh_3 and PBu_3, but surprisingly when the Fmoc protecting group was used (**2.90**), only the PPh_3 method produced

the desired result, while the PBu_3 caused deprotection of the Fmoc protecting group. The deprotection mechanism of Cbz (**Scheme 29**) and Fmoc (**Scheme 30**) protected amines differ significantly and play an important role in our findings.



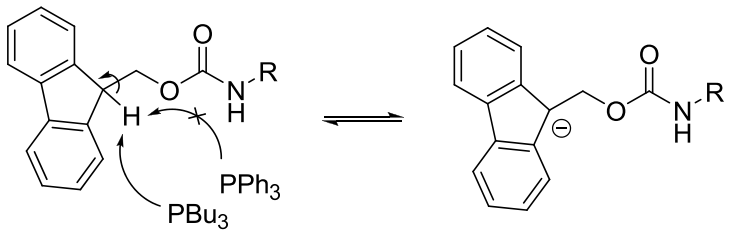
Scheme 29. Deprotection of Cbz protected amine.



Scheme 30. Deprotection of Fmoc protected amine.

The deprotection of Cbz requires a strong acid such as HBr or hydrogenation, whereas the Fmoc is stable to these conditions because neither S_N1 nor S_N2 can occur at the CH_2 carbon. PPh_3 has a pK_aH of 2.73 while PBu_3 has a pK_aH of 8.43. Fmoc cleavage is usually achieved with a number of bases, including most notably piperidine which has a pK_a of 11.24 and ethanolamine which has a pK_a of 9.50. Surprisingly the PBu_3 must be acting as a strong enough base in the reduction reaction to cause the Fmoc group to be removed (**Scheme 31**). PPh_3 on

the other hand is not basic enough to cause deprotection of the Fmoc group and hence the reduction of the cystine will proceed.

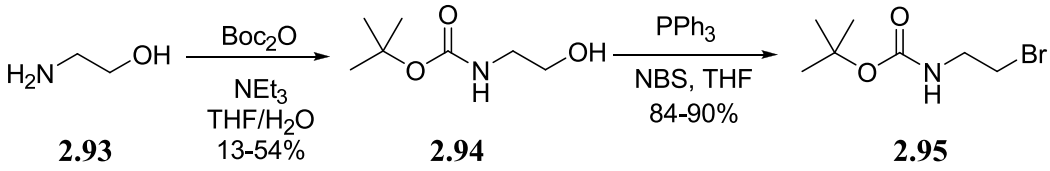


Scheme 31. Reaction of Fmoc with PPh_3 and PBu_3.

As eluded to earlier, due to this finding and the fact that the Fmoc compound (**2.90**) decomposed on the column and had to be recrystallised giving lower yields, the Cbz protecting group was preferred. All subsequent reactions were carried out using Cbz as the preferred protecting group. Although, it should be noted that it is possible to reduce the Fmoc protected cystine using PPh_3 and mercaptoethanol to form the desired Fmoc protected cysteine (**2.92**), albeit with a lower and less reliable yield.

2.3.3 Protected Bromoethylamine

The synthesis of *N*-Boc-2-bromoethylamine (**2.95**) was first carried out by Boc protecting ethanolamine (**2.93**) using triethylamine in THF and water (**Scheme 32**). The Boc protected ethanolamine was then subjected to a substitution reaction using *N*-bromosuccinimide and PPh_3, furnishing the desired organic halide (**2.95**). It should be noted that mesylation of alcohol **2.94** was carried out, but coupling in the next stage of the synthesis was unsuccessful and therefore abandoned. The synthesis of organic bromides and coupling was our preferred method.

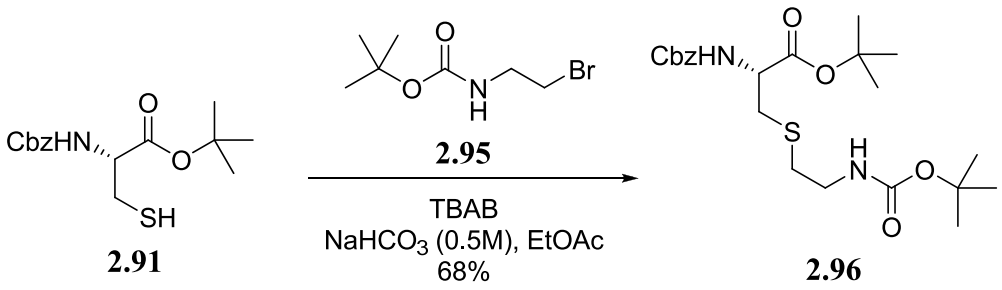


Scheme 32. Synthesis of Boc-protected bromoethylamine.

The synthesis of *N*-Boc-2-bromoethylamine by the above method gave mixed results and yields of final product (**2.95**), especially in the Boc protection of ethanolamine to form the Boc-protected species **2.94**. Starting from the commercially available *tert*-butyl-*N*-(hydroxyethyl)carbamate (**2.94**) and carrying out the bromination step simplified our synthesis, giving greater yields of protected bromoethylamine. The synthesis from commercially available Boc-protected ethanolamine derivatives was therefore preferred, although the complete synthesis from simple ethanolamine derivatives, and the one shown in **Scheme 32**, is much more general and is the preferred synthesis when substituted Boc protected amines are not commercially available.

2.3.4 Coupling Reaction - Thialysine Derivative

Following the synthesis of *N*-Boc-2-bromoethylamine (**2.95**) and with the suitably protected Cbz cysteine (**2.91**) in hand, the coupling of these reagents was now possible. This was achieved in reasonable yields using a bi-phasic reaction with tetra-*N*-butylammonium bromide (TBAB) as the phase-transfer catalyst in EtOAc and aqueous $NaHCO_3$, furnishing the desired thialysine derivative (**2.96**).

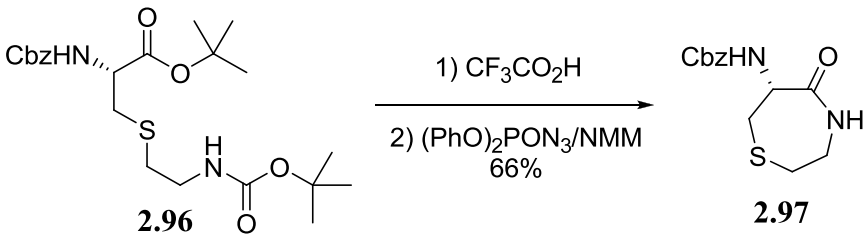


Scheme 33. Formation of the thialysine derivative *via* coupling.

2.3.5 Deprotection and Ring Closure

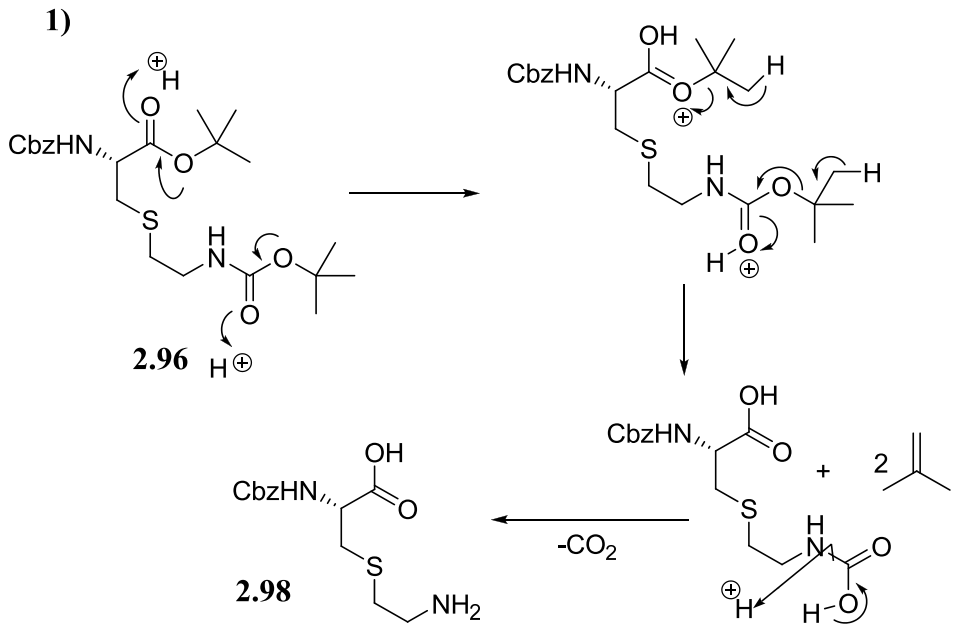
The thialysine derivative (**2.96**) could now be de-protected selectively and cyclised to produce the desired Cbz-protected caprolactam (**2.97**, **Scheme 34**).

Removal of the protecting groups was achieved using trifluoroacetic acid (TFA) followed by intramolecular condensation using diphenyl phosphorazidate ($(PhO)_2P(O)N_3$).

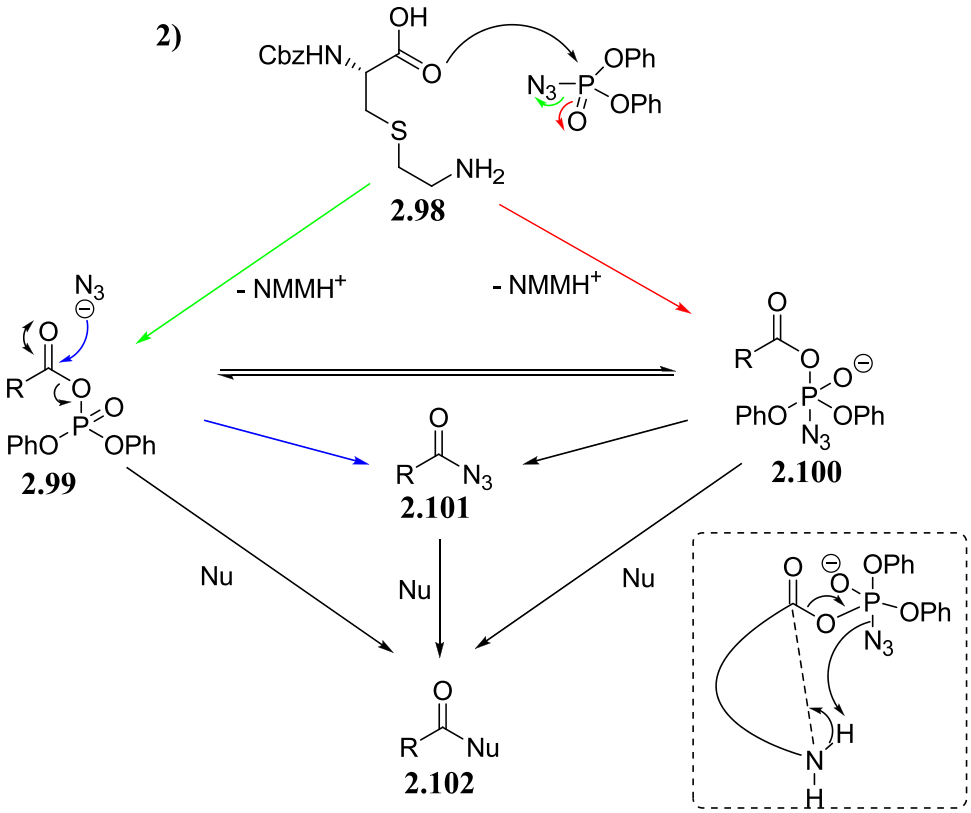


Scheme 34. Deprotection and ring-closure to form the Cbz-protected thialactam

The reaction mechanism for the deprotection and ring closure using TFA and $(PhO)_2P(O)N_3$ are shown below in **Scheme 35** and **Scheme 36**.[174-175]



Scheme 35. Boc-deprotection of thialysine derivative with TFA.

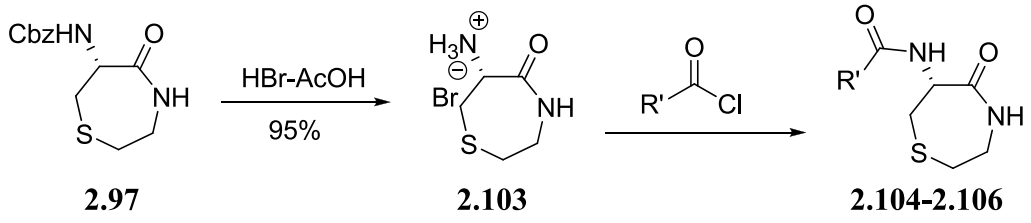


Scheme 36. Ring closure of thialysine derivative with $(PhO)_2P(O)N_3$.

During the first step both ^{t}Bu ester and Boc groups would be displaced from our thialysine derivative (**2.96**) forming the intermediate (**2.98**) (which was not purified). In the second step the carboxylic acid oxygen would attack the phosphorus atom in $(PhO)_2P(O)N_3$ to give two possible acyl phosphates, **2.99** and **2.100**. The acyl azide (**2.101**) would be formed by a S_N2 type reaction of (**2.99**) with the azide anion or S_N1 type rearrangement of (**2.100**). Intramolecular reaction of the amine with the acyl phosphates as well as the acyl azide would form the lactam (**2.102**). All routes are likely to occur, although the predominant route is most likely the acyl phosphate (**2.100**) reacting with the amine (as shown in the dotted box in **Scheme 36**) as studies *via* the Young racemization test have suggested a concerted transition state.[175] This amide bond formation is the *N*-acylation of the amine as a nucleophile. If there is no nucleophile, the reaction will stop at the stage of the acyl azide (**2.101**), which will thermally undergo the Curtius rearrangement to furnish the isocyanate.

2.3.6 Deprotection and Acylation

Lactam **2.97** was easily deprotected with HBr to produce the hydro-bromide salt (**2.103**). A number of acylations were carried out directly on the salt to produce the desired 1,4-thiazepin-5-one derivatives (**Scheme 37**).



2.97 **2.103** **2.104-2.106**

Scheme 37. Deprotection and acylation. The final steps in the synthesis of thialactams.

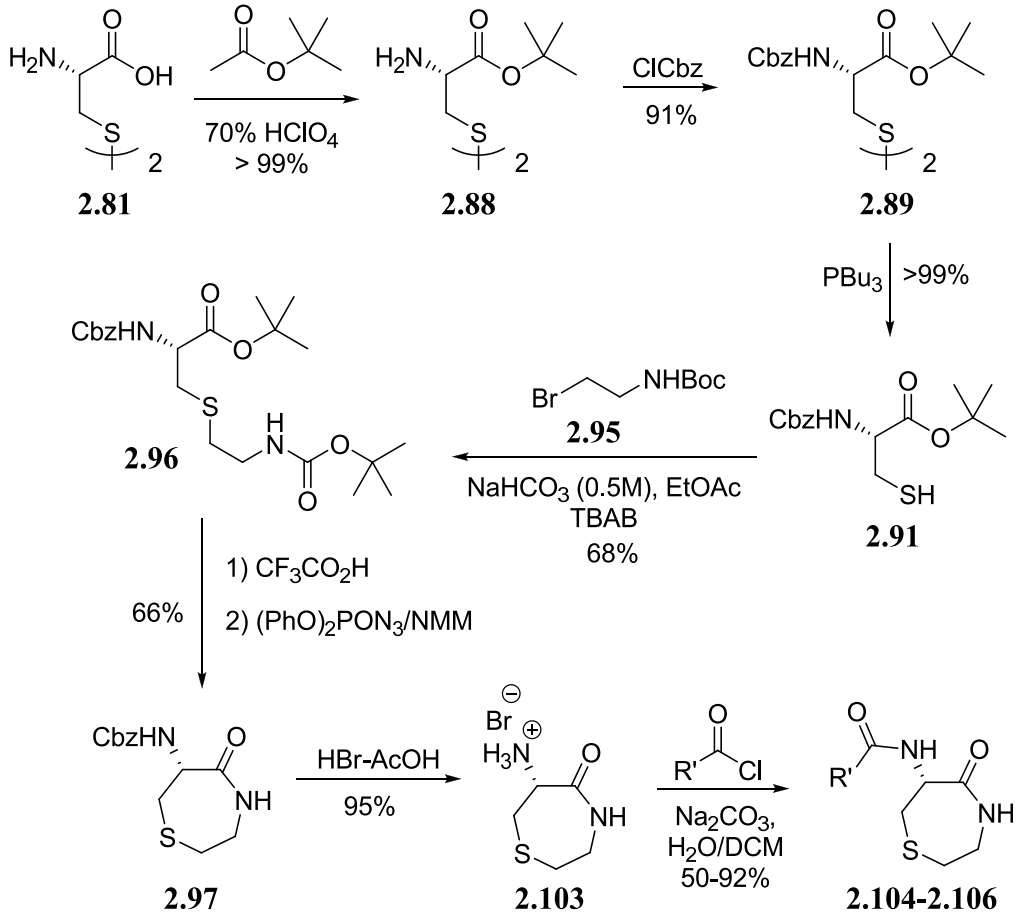
Entry	***R´***	***Yield (%)***
(**2.104**)	$^{t}Bu^{*}$	50
(**2.105**)	Adamantane*	92
(**2.106**)	$CH_3(CH_2)_9C(CH_3)_2$*	57

Table 2. Acylation of **2.103**. *Synthon of acid chloride.

The acylation step was carried out with 3 side chains: ^{t}Bu, adamantane and 2,2-dimethylundecane (**Table 2**). These were selected because in previous experiments with analogous structures, ^{t}Bu gave the best biological results, adamantane gives a crystalline product, and similarly good biological results, and the long chain was selected because it is known to inhibit the chemotaxis of THP-1 cells and human polymorphonuclear cells induced by other CC and CXC chemokines in biological testing.[90,96-98] All of these can then be compared with their analogous non-sulfur containing compounds which have previously been synthesised to see the effect (if any) of replacing one CH_2 in the ring with a sulfur atom.

2.4 Summarised Approach to Asymmetric γ-Thialactams

The complete synthesis of the thialactams is shown below in **Scheme 38**.



Scheme 38. Summarised approach to thialactams.

This modular approach was repeated successfully and was therefore the chosen synthetic route for the synthesis of the thiazepan-5-ones.

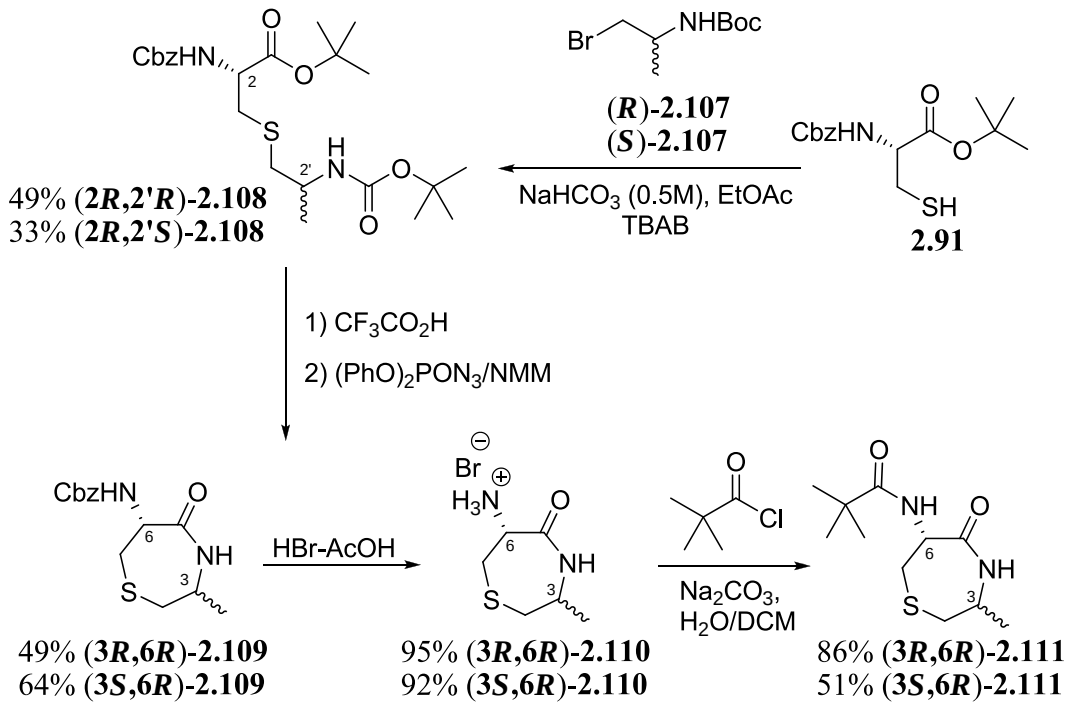
2.5 Expanding the library

With the simple caprolactams (**2.104**-**2.106**) synthesised and the synthetic route realised (**Scheme 38**) the library of compounds could then be extended. The same approach as the simple caprolactam was employed with the protected cysteine

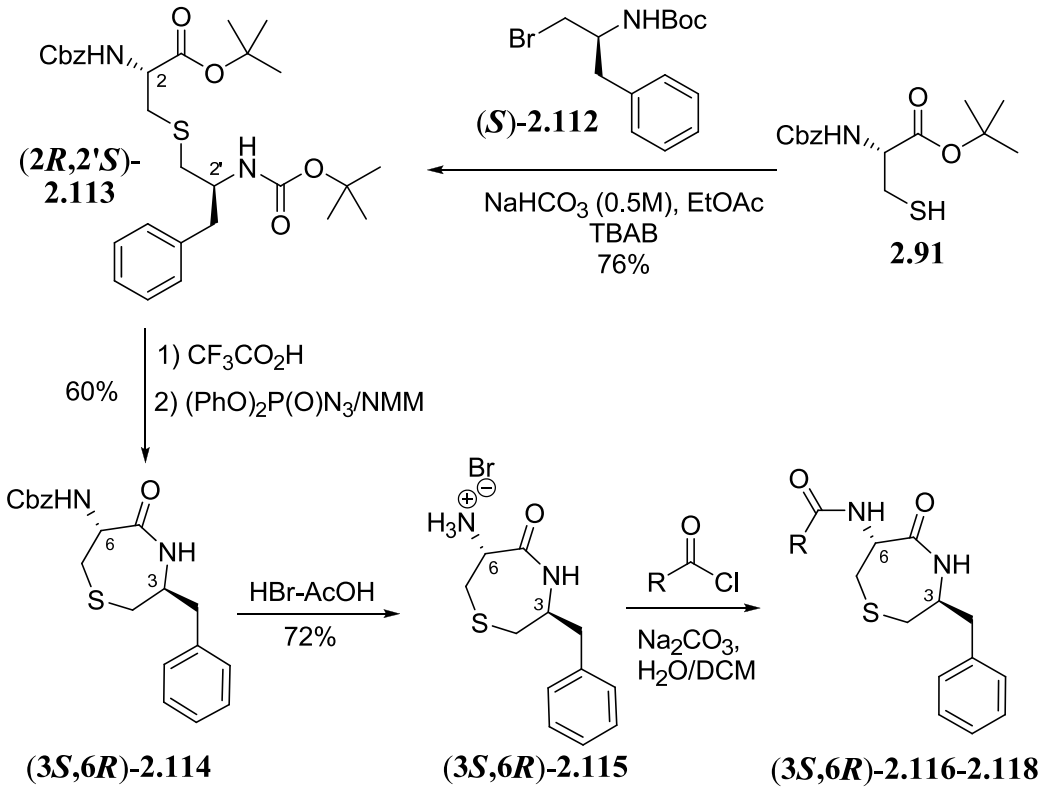
(**2.91**) being coupled together with suitably substituted bromoethylamine derivatives instead of *N*-Boc-2-bromoethylamine (**2.95**).

2.5.1 3-Substituted Thialactam Derivatives

The synthesis of the 3-methyl-thiazepin-5-one family and 3*S*-benzyl-thiazepin-5-ones are shown in **Scheme 39** and **Scheme 40** respectively. The methyl substituted bromine compounds (**2.107**) were easily prepared by the bromination of commercially available (*R*)-*N*-Boc-alaninol and (*S*)-*N*-Boc-alaninol, as described for the synthesis of protected bromoethylamine (**Scheme 32**) previously. Similarly, the benzyl derivative, (***S***)-**2.112**, was synthesised from the available L-phenylalaninol, although the synthesis of its enantiomer (and hence the diastereoisomers of (**3*S*,6*R***)-**2.116-2.118**) was more of a challenge. The NMRs of all isolated compounds contained only one diastereoisomer.



Scheme 39. Synthesis of the 3-methyl-thiazepin-5-one derivatives.

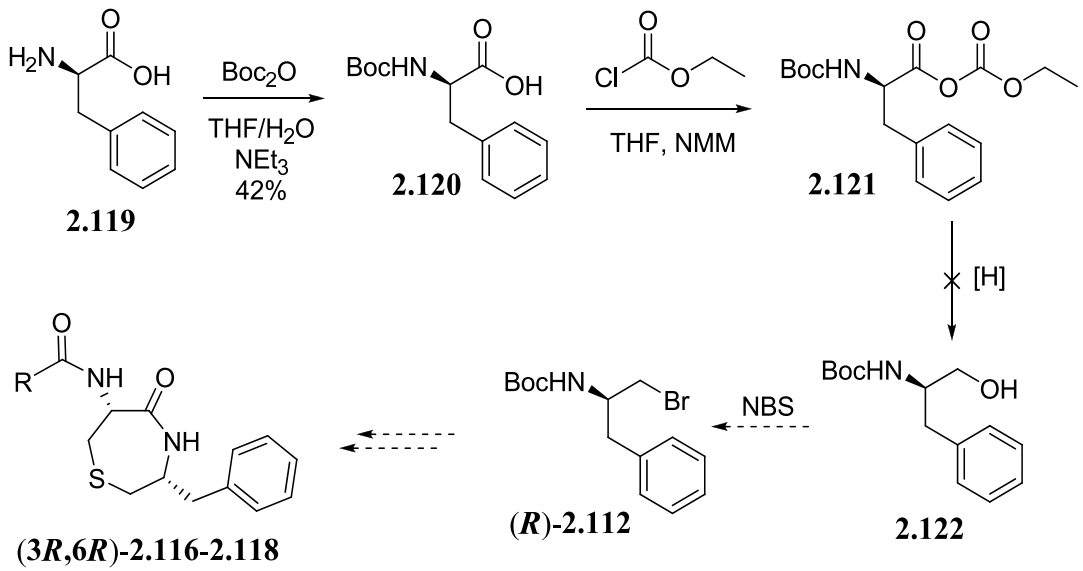


(X)	*R*	*Yield (%)*
(**3S,6R**)-**2.116**	^{t}Bu	74
(**3S,6R**)-**2.117**	1-Adamantane	33
(**3S,6R**)-**2.118**	$CH_3(CH_2)_9C(CH_3)_2$	65

Scheme 40. Synthesis of the 3-benzyl-thiazepin-5-one derivatives.

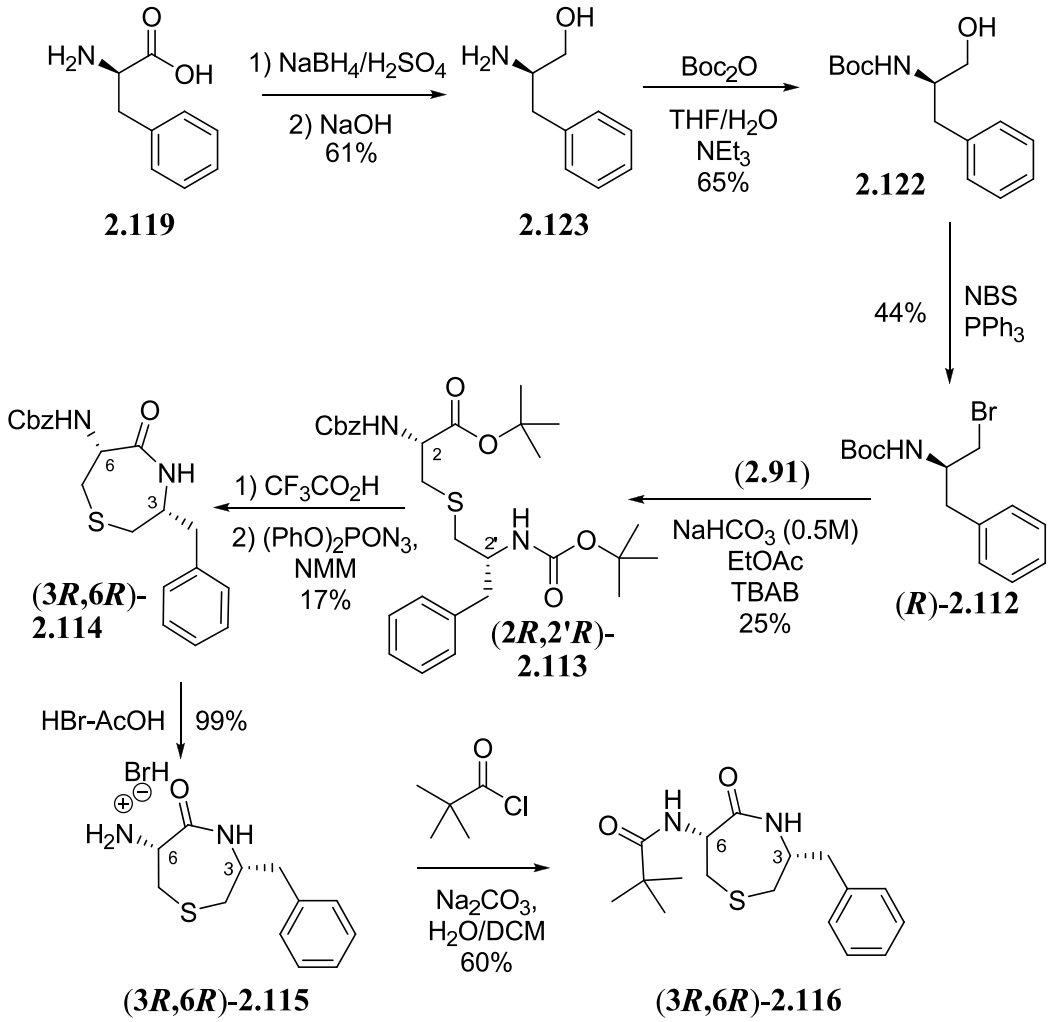
2.5.2 Diastereoisomer of Benzyl-Thialactam

Attempts to synthesise the enantiomer of (***S***)-**2.112** *via* an alternative method, the Boc protection of *D*-phenylalanine (**2.119**) and subsequent transformations (**Scheme 41**), failed. It was thought that the Boc protected anhydride of *D*-phenylalanine (**2.121**) could be reduced and brominated to the desired bromoethylamine derivative (***R***)-**2.112**, but problems occurred during the reduction of the anhydride. Any attempt to reduce the anhydride with sodium borohydride failed and an alternative method was sought.



Scheme 41. Original attempt in the synthesis of (R,R)-benzyl-thialactams.

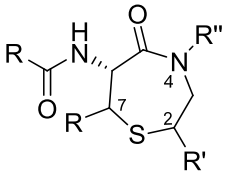
The alternative route to the bromethylamine agent (***R***)-**2.112** utilised a modification of the Abiko method (**Scheme 42**).[176] This involved reduction of *D*-phenylalanine to the corresponding alcohol (**2.123**) with the *in situ* generation of borane (BH_3) followed by the addition of aqueous sodium hydroxide. With the synthesis of this alcohol, bromo-compound (***R***)-**2.112** could easily be synthesised *via* Boc protecting and brominating (*vide supra*). Finally, the (*R*,*R*)-benzyl-thialactam was synthesised by coupling the suitably protected cysteine residue (**2.91**) by the same procedure as its diastereoisomer.



Scheme 42. Synthesis of (*R*,*R*)-benzyl-thiazepin-5-one derivative *via* a modified Abiko method.

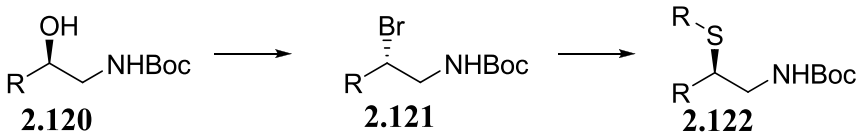
2.5.3. Proposed route to 2, 4 & 7-Substituted Thialactam Derivatives

The synthesis of 2, 4 and 7 substituted thiazepan-5-ones (**2.119**) could be envisaged in a similar manner *via* the same modular approach as previous thialactams. The synthesis of 2 substituted thialactams would require for instance a bromethylamine agent such as **2.121** derived from its corresponding alcohol (**2.120**) as shown in **Scheme 43**. The two S_N2 reactions would mean that the original stereochemistry of the alcohol starting material would be retained in the final synthesis of the lactam ring.



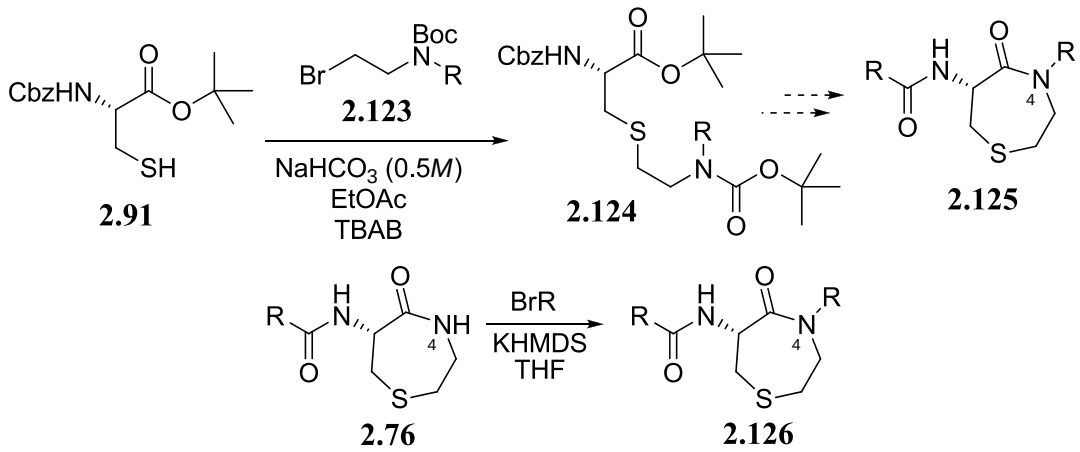
2.119

The synthesis of the *N*-4 substituted derivatives of the thiazepan-5-one can be realised by beginning the synthesis with a suitable bromoethylamine agent (such as (**2.123**)) and coupling with the cysteine residue (**2.91**), which I have shown to be successful for *N*-methyl. Continuing the synthesis as before (*vide supra*) would generate the desired lactams (**2.125**). Alternatively, *N*-4 substituted derivatives could be realised by the direct conversion of the unsubstituted thiazpean-5-one (**2.76**) *via N*-alkylation, for which there is literature precedent.[149,177]



2.120 **2.121** **2.122**

Scheme 43. Proposed route to 2-substituted thialactams.

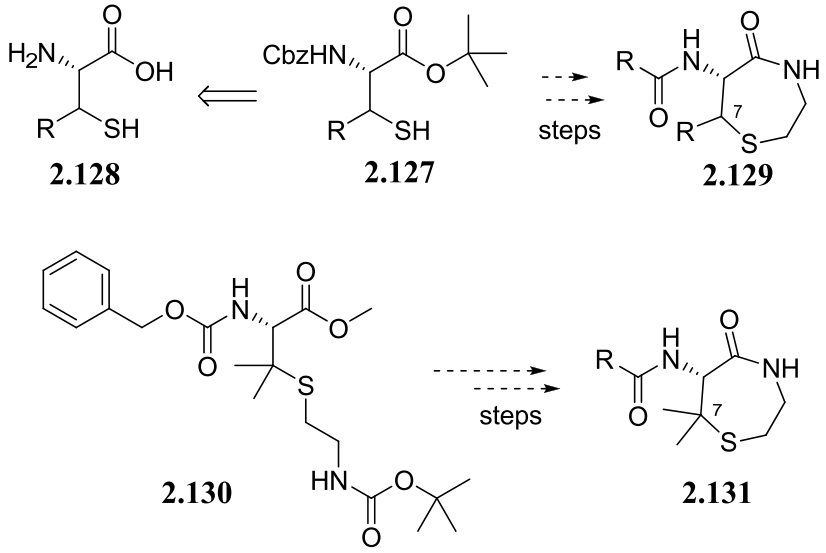


2.91 **2.123** **2.124** **2.125** **2.76** **2.126**

Scheme 44. Synthetic route to 4-substituted thialactams.

7-Substituted lactams could again be synthesised in a similar manner by beginning with substituted cysteine derivatives (**2.127**) and applying the same methodology. Indeed, I have shown that methyl protected penicillamine can be

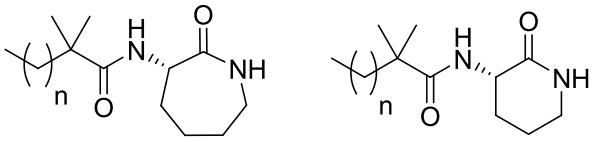
used together with *N*-Boc-2-bromoethylamine (**2.95**) to generate **2.130**. Deprotection and ring closure should furnish the 7-substituted lactams.



Scheme 45. Synthetic route to 7-substituted thialactams can be realised from substituted cysteine derivatives (top) proven possible by the synthesis of **2.130** (bottom). Subsequent steps were not carried out.

2.6 Long Chain Investigation

As previously explained the synthesis of long chain compounds ((**2.106**) and (**3*S*,6*R***)-(**2.118**)) were carried out because we knew that the 2',2'-dimethyldodecane side chain attached to lactams is key to the inhibition of the chemotaxis of THP-1 cells and human polymorphonuclear cells induced by other CC and CXC chemokines.[96-98] For consistency and comparison, these long chain dimethyl compounds were synthesised with the thiazpin-5-one derivatives. We know from previously published research by the Fox group that 2',2'-dimethylated compounds are very potent, but there were gaps in our literature which needed investigating.[96-98] Fox had synthesised 2',2'-dimethylated compounds of type **2.132** and **2.133** where n is equal to 9, 2, 1 and 0, but a systematic approach was never employed to see what size chain gave the best biological results.

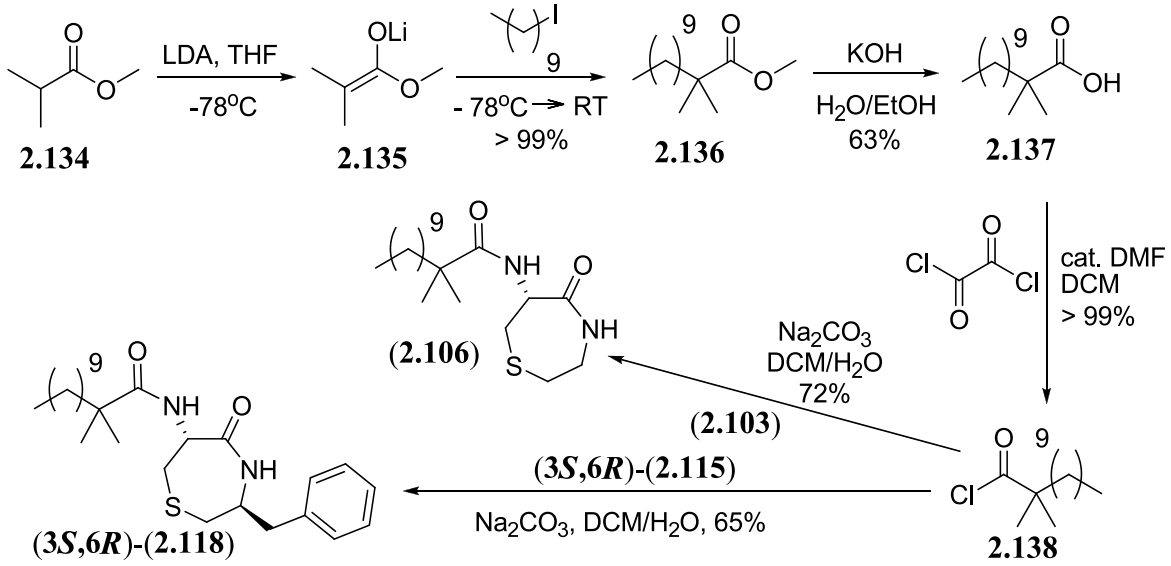


2.132 **2.133**

It was therefore necessary to synthesise the full set of side chains filling the gaps in the literature, thus optimising the side chain length. The 2',2'-dimethyldodecanoylamino thiazepan derivatives (**2.106**) and (**3*S*,6*R***)-(**2.118**) were first synthesised and with the preferred synthetic scheme established the whole set of long chains could be synthesised. The 2-pyridone head group (**2.162**) instead of the caprolactam (**2.103**) was used as a large quantity of the 2-pyridone was easily synthesised.

2.6.1. 2',2'-Dimethyldodecanoylamino Thialactam Derivatives

The synthetic route to the 2'2'-dimethyldodecanoyl derivatives is shown below in **Scheme 46**. Alkylation of decyl iodide with the lithium enolate of methyl isobutyrate (**2.134**) and base hydrolysis of the methyl ester were carried out with only simple work up procedures (*vide infra*). Purification of the long chain acid (**2.137**) to give clean product was carried out before the acid chloride was reacted with the appropriate thiazepin salt. The acid chloride was once isolated on a small scale for analysis, otherwise it was reacted immediately to give the final product.



Scheme 46. Synthetic route to the 2'2'-dimethyldodecanoyl thialactam derivatives.

2.6.2 Purification Process to the Synthesis of 2'2'Dimethyldodecanoic Acid

During the synthesis of the 2'2'-dimethyldodecanoic acid (**2.137**) from the synthetic approach above it would not be unreasonable to expect impurities from the alkylation or the hydrolysis steps. An excess of methyl isobutyrate (**2.134**) ensures that all of the iodo-species is consumed (confirmed by NMR). Therefore, during the hydrolysis step, the only other impurity would be another acid. A simple work up procedure to eliminate any acid impurities and avoid the need for chromatography or distillation was adopted and is discussed herein.

Using the Henderson-Hasselbalch equation (**Equation 1**) and re-writing it using the power laws we can then think about the partition coefficient of our substance during the work up procedure to come up with an equation which will help us in the purification.

$$pH = pK_a - \log\left(\frac{[acid]}{[base]}\right) \equiv \frac{[acid]}{[base]} = 10^{pK_a - pH}$$

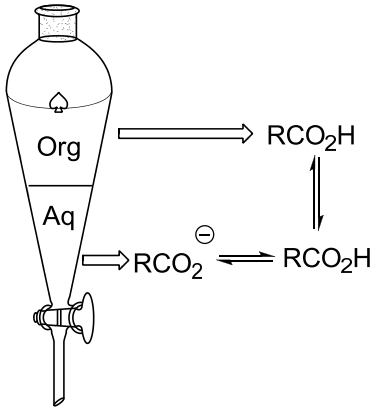
Equation 1. Henderson-Hasselbalch equation rearranged.

The partition coefficient, or distribution coefficient, is defined as the ratio of concentrations of a compound in the two phases of a mixture of two immiscible solvents at equilibrium (**Equation 2**).

$$P = \frac{[acid]in\ organic\ phase}{[base]in\ organic\ phase}$$

Equation 2. Partition coefficient of a species P.

Considering our bi-phasic mixture, we know that the percentage of acid in the organic layer during the work up procedure will be the amount of acid in the organic layer divided by the total amount as shown in **Figure 12**.



$$\%\ acid\ in\ organic\ phase = \frac{[RCO_2H_{(org)}]}{[RCO_2H_{(org)}] + [RCO_2^-{}_{(aq)}] + [RCO_2H_{(aq)}]} \times 100$$

Figure 12. Equation showing the percentage of acid in the organic phase. By considering a bi-phasic work up (top) we can calculate the percentage of acid in the organic layer by considering the amount of acid in the organic layer divided by the whole (bottom).

Substituting our partition coefficient equation and our re-arranged Henderson-Hasselbalch equation into the above equation we can calculate the percentage of acid in the organic layer if we know the pK$_a$, pH and partition coefficient of our substance with this new equation (Equation 3).

$$y = \frac{P \times 10^{(pK_a - pH)}}{1 + 10^{(pK_a - pH)} + P \times 10^{(pK_a - pH)}}$$

Equation 3. % of acid in an organic phase during a work up.

The isobutyrate impurities and our long chain 2'2'dimethyldodecanoic acid will probably have a similar pK$_a$ (~5), therefore when the pK$_a$ and pH of our

substances are the same the percentage of acid in the organic phase will be equal to 50% (because the Henderson-Hasselbalch equation will be reduced to 1). In reality the partition coefficient for our long chain will be far different from the partition coefficient of the isobutyrate impurity. Our long chain will be very hydrophobic and therefore its partition coefficient will be very high, much greater than the shorter isobutyrate. If we assume that our partition coefficient for the 2'2'dimethyldodecanoic acid is approximately 10000 and our partition coefficient for our impurity is roughly 5 (which is a reasonable estimate for both) then we can plot a graph from our equations (**Figure 13**).

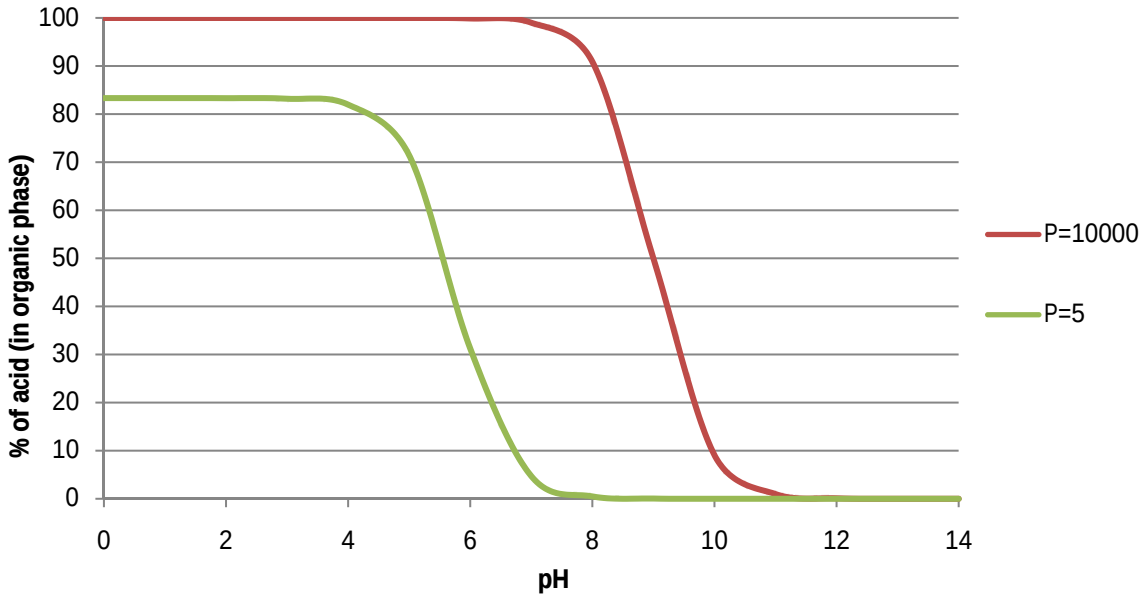


Figure 13. A plot of the percentage of acid in the organic phase during a separation for our 2'2'-dimethyl substances. The red line is representative of the long chain 2'2'dimethyldodecanoic acid. The green line is representative of the methyl isobytyric acid.

From the 2 plotted lines in **Figure 13** we can see that the "apparent" $p\mathrm{K_a}$ ($'p\mathrm{K_a}$) has shifted. When the partition coefficient is very high, like in this case, we can think of the apparent $p\mathrm{K_a}$ of our substance being similar to that of **Equation 4**.

$$'pK_a = pK_a + \log(P - 1)$$

Equation 4. The apparent *p*Ka of a compound.

The apparent *p*K_a of our isobutyrate has increased slightly, but not as much as the 2'2'dimethyldodecanoic acid. It is not hard to see that if we keep the *p*H to 8 or above we can get the maximum amount of 2'2'dimethyldodecanoic acid with no isobutyrate impurities. This technique of keeping the *p*H to ~8.0 was carried out and the procedure worked extremely well. The ^{1}H NMR spectra of the crude ester (**2.136**) and final 2'2'dimethyldodecanoic acid (**2.137**) are shown below in **Figure 14** and **Figure 15** respectively.

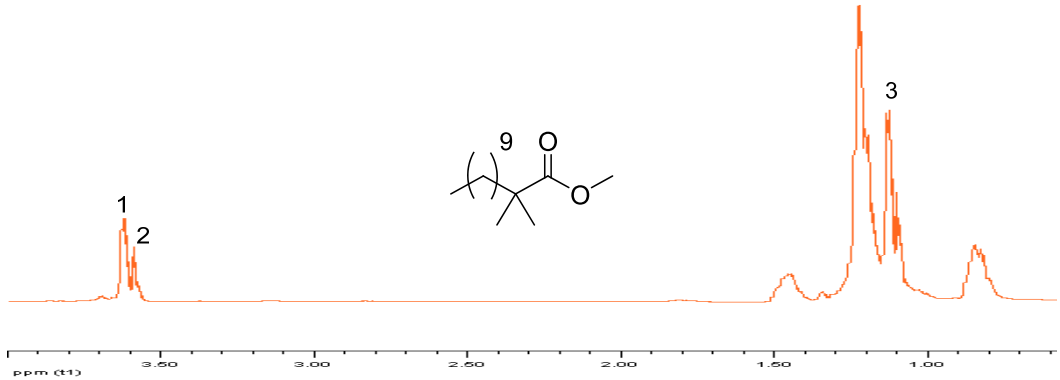


Figure 14. ^{1}H NMR of crude (**2.136**). It is possible to see the isobutyrate impurity in the ^{1}H NMR as there are two ester peaks (peak 1 and 2). There are also two peaks for the methyl groups (labelled peak 3) corresponding to desired product and impurities.

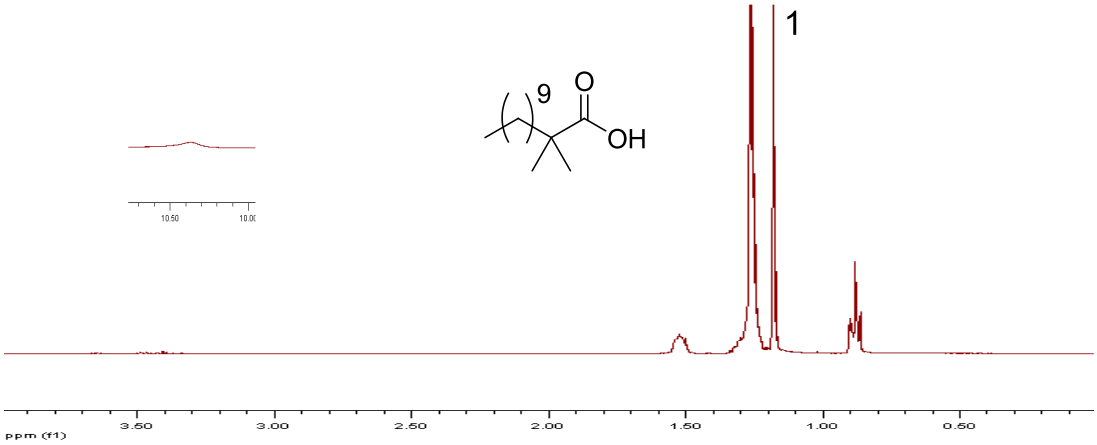
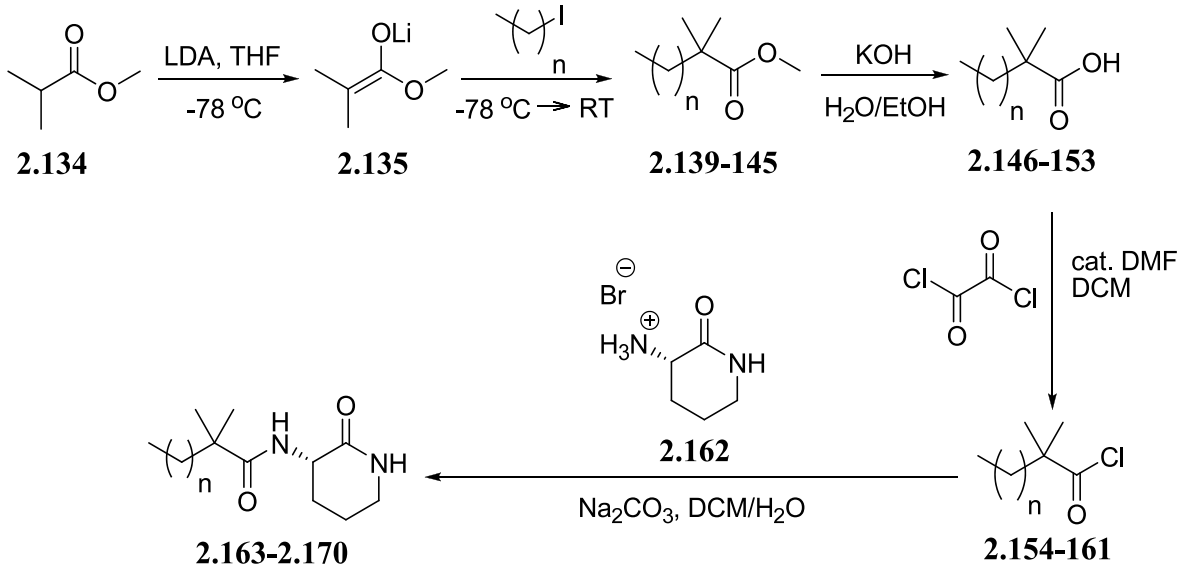


Figure 15. ^{1}H NMR of (**2.137**). Keeping the pH to 8 after the hydrolysis gives clean product with no ester or isobutyrate impurities (as seen by the single peak at peak 1 and the disappearance of the ester peaks).

In the crude ester ^{1}H NMR (**Figure 14**) isobutyrate impurities are apparent while the final acid ^{1}H NMR there are no significant impurities (**Figure 15**).

2.6.3 δ-Lactam Side Chain Investigation

Adopting the same techniques that were used for the 2'2'-dimethyldodecanoic acid thiazepan derivatives, the full set of 2'2'-dimethyl side chains, with a δ-lactam (or piperidin-2-one) as the head group, were synthesised (**Scheme 47**). The synthesis with the piperidin-2-one (**2.162**) was used because it was quick, facile and available in large quantities, as well as their having been a wide range of piperidinone compounds already tested (*vide supra*).



(X)	*n*	*Yield (%)*	*(X)*	*n*	*Yield (%)*
2.139	8	>99	**2.155**	7	>99
2.140	7	>99	**2.156**	6	97
2.141	6	>99	**2.157**	5	>99
2.142	5	>99	**2.158**	4	>99
2.143	4	99	**2.159**	3	98
2.144	3	63	**2.160**	2	99
2.145	2	78	**2.161**	1	96
2.146	8	84	**2.163**	8	16
2.147	7	81	**2.164**	7	31
2.148	6	69	**2.165**	6	17
2.149	5	94	**2.166**	5	14
2.150	4	47	**2.167**	4	41
2.151	3	8	**2.168**	3	34
2.152	2	3	**2.169**	2	7
2.153	1	NA	**2.170**	1	0.6
2.154	8	98			

Scheme 47. δ-lactam long chain synthesis. Investigation into the chain length requirement.

2.7 Biological Assays

Compounds were subjected to two different biological assays, an SSTR2 binding assay and a leukocyte migration assay. SSTR2 binding data was obtained by Tilly Sharp at Total Scientific (Babraham Research Campus, Cambridge) using a technique called fluorescence polarisation (FP). Leukocyte migration data was determined by Dr Jill Reckless of the Department of Medicine at the University of Cambridge, using a multi-well filter migration assay system protocol.

2.7.1 Fluorescence Polarisation (FP)

FP is a technique used to study molecular interactions. Experiments are done in solution allowing true equilibrium analysis and measurements do not degrade the sample, so they can be treated and re-analysed. FP also allows real time measurements to generate kinetic assays, is insensitive to variations in concentration and is an optimal technique for homogeneous assay formats.[178]

When fluorescent molecules in solution are excited with plane-polarised light, they emit light back into the same plane if the molecules remain stationary during the excitation of the fluorophore. This observation by Perrin is the basis of the theory of FP.[179-183] In reality, molecules rotate and tumble and the planes into which the light is emitted can be very different from the plane used for initial excitation. If the polarised light used for excitation is vertical then the emitted light in the horizontal and vertical planes can be monitored. If the molecule is very large then little movement will take place during excitation and the polarised light emitted will remain highly polarised. However, if the molecule is small then the rotation of the molecule is faster and the polarised light emitted will be less than in the excitation plane (the light becomes depolarised). The FP of

fluorophore labelled somatostatin bound to SSTR2 can be compared to that which has been displaced by a test compound (**Figure 16**).

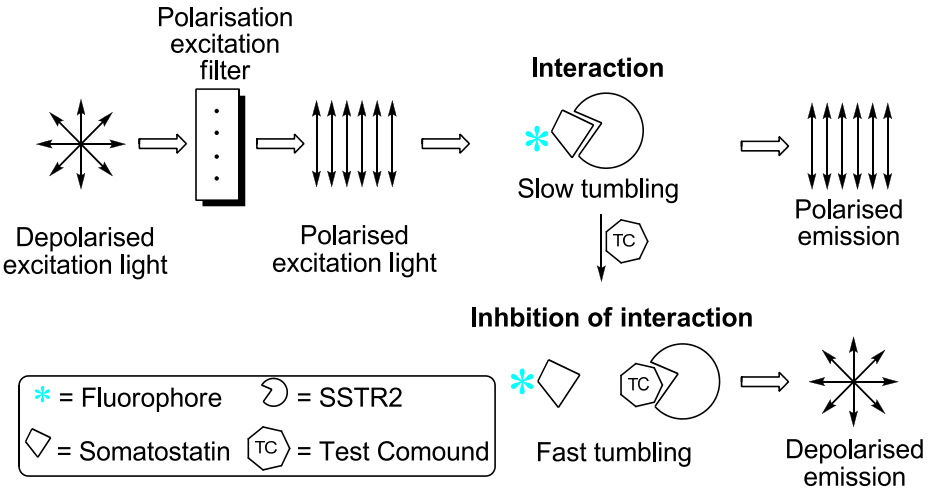


Figure 16. Principles of the fluorescence polarisation assay.

If a test compound displaces somatostatin, the non-bound somatostatin will cause the emission of depolarised light. Conversely, if the compound does not displace somatostatin, the emitted light will remain polarised.

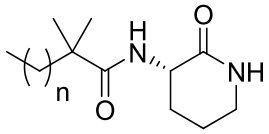
2.7.2 FP Results

2.7.2.1 Long Chain Investigation Results

The long chain compounds, **2.163-2.170**, were tested using FP techniques for their SSTR2 binding activity at a concentration of 100 μM. The FP assay was run following a standard protocol with the polarisation calculated from the emitted light measured in the vertical and horizontal planes. The data is given as a percentage inhibition of SS-14 FITC from SSTR2, as summarised in **Table 3**.

The results clearly show that competitive binding occurs when the chain length is eleven carbons long, with almost 50% inhibition. Full inhibition occurs when the

chain length is twelve carbons long. Aside from the 2',2'-dimethyldodecane side chain, none of the other compounds show any displacement of somatostatin.



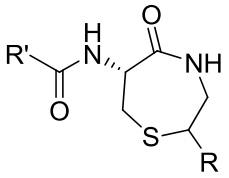
2.160-2.169

(X)	*n*	*Inhibition (%)*	*Corrected Inhibition (%)*
2.171*	9	N/A	99
2.163	8	39	46
2.164	7	-21	-20
2.165	6	-5	-2
2.166	5	-5	-16
2.167	4	-7	-6
2.168	3	-5	-5
2.169	2	-70	-72
2.170	1	-7	-7
2.172*	0	N/A	10

Table 3. FP results of long chain piperidinones. *Compound previously synthesised by D.J.Fox and shown here for comparison.

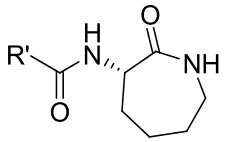
2.7.2.2 Thialactam FP Results

The thialactams synthesised were also tested for their SSTR2 binding activity *via* the same protocol as the long chain piperidinones, the results of which are shown in **Table 4**. For comparison the results found for analogous non-sulfur containing lactams are shown in **Table 5**, as previously determined by the Fox group.



(X)	*R´*	*R*	*Inhibition (%)*	*Corrected Inhibition (%)*
2.104	^{t}Bu	H	-3	-2
2.105	Adamantane	H	-8	-10
2.106	$CH_3(CH_2)_9C(CH_3)_2$	H	108	114
(3*R*,6*R*)-2.111	^{t}Bu	Me	-11	-10
(3*S*,6*R*)-2.111	^{t}Bu	Me	-23	-16
(3*S*,6*R*)-2.116	^{t}Bu	Bn	-21	-19
(3*S*, 6*R*)-2.117	Adamantane	Bn	-15	-6
(3*S*,6*R*)-2.118	$CH_3(CH_2)_9C(CH_3)_2$	Bn	94	107

Table 4. FP results of thilactams synthesised.



(X)	*R´*	*Corrected Inhibition (%)*	*Leukocyte Migration Inhibition ED_{50} (nM)*
2.2	^{t}Bu	6	0.04
2.173	Adamantane	21	0.09
2.174	$CH_3(CH_2)_9C(CH_3)_2$	107	0.09

Table 5. FP and leukocyte migration results of caprolactams previously synthesised by D.J.Fox.

It can be seen from the results that the long chain dimethyl compounds **2.106** and (**3*S*,6*R***)-**2.118** are unaffected by the inclusion of the sulfur atom or a benzyl side chain attached to the ring, with similar inhibition of somatostatin for the thialactams as the analogous caprolactam (**2.174**). Including sulfur decreases the inhibition for smaller side chains, with the adamantane side group being affected the most. The inclusion of a side group on the thialactam also decreases its inhibition ability, with the general trend of a bulkier side group (H>Me>Bn) giving a progressively worse result.

2.7.3 Leukocyte Migration

A multi-well filter migration assay system (**Figure 17**) was used to determine leukocyte migration.[62] Each upper chamber in the migration assay contained leukocyte and inhibitor (motile cells), while the test substance containing fluid (or chemoattractant) was placed in the lower chamber. The upper and lower chambers were separated by a suitably porous filter allowing cell migration in the direction of the concentration gradient (from the upper chamber to the lower chamber).

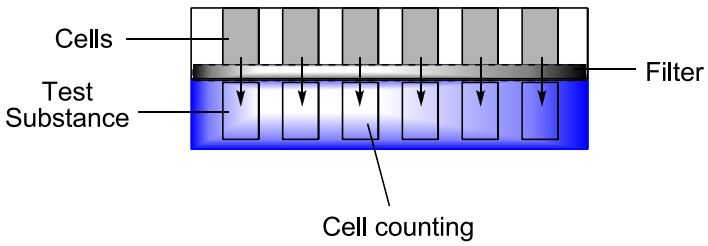
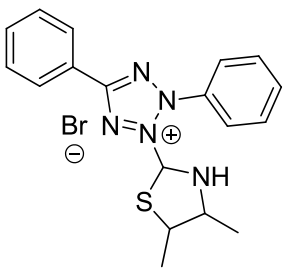
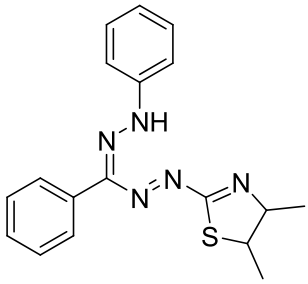


Figure 17. Illustration of a multi-well filter migration assay.

The migrated cells were quantified using the yellow dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, **2.175**). In the presence of reductases MTT is reduced to a purple formazan (**2.176**). The concentration of reductases is related to the number of living cells, so measuring the amount of formazan is a way of determining the number of living cells. Leukocyte migration data was determined by Dr Jill Reckless of The Department of Medicine at The University of Cambridge in this way, and determined as percentage inhibition of neutrophil migration at a given concentration.



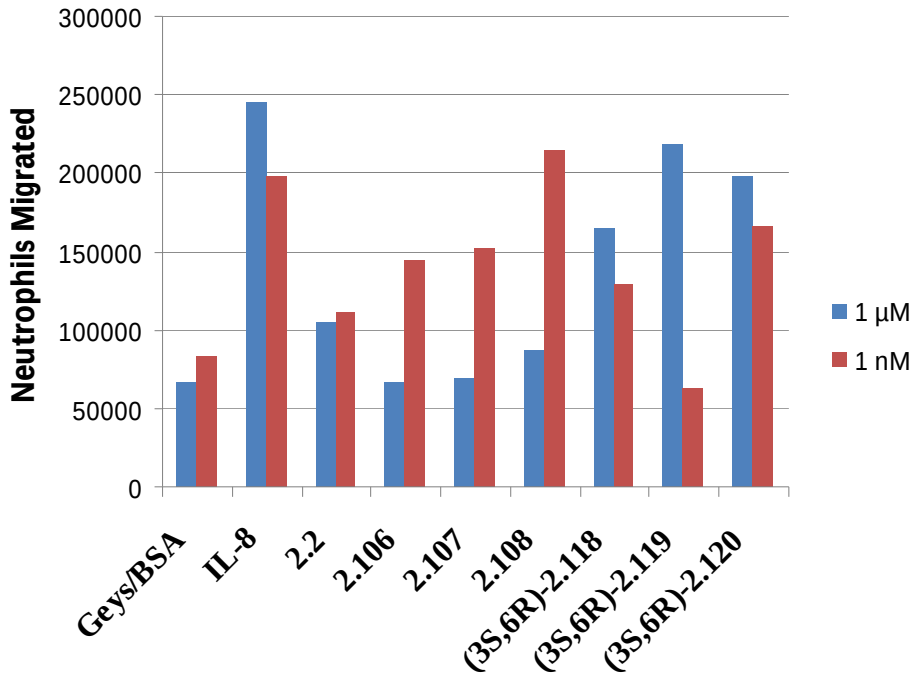
2.175



2.176

2.7.3.1 Leukocyte Migration Results

Results for the thialactams **2.104**-**2.106** and (**3*S*,6*R***)-**2.116**-**2.118** are shown below in **Graph 1**. It can be seen from the results that the simple thialactams **2.104**-**2.106** show very strong inhibition at μM concentrations, and are comparable to the analogous caprolactam **2.2**. At nano molar concentrations the compounds do not have the same effect as caprolactam **2.2**. As for the substituted thialactams (**3*S*,6*R***)-**2.116**-**2.118**, inhibition occurs but not as potent as their unsubstituted counterpart. Data for these compounds at nM concentrations give inconsistent results.



Graph 1. Leukocyte migration results of compounds **2.106**-**2.108** and (**3*S*,6*R***)-**2.118**-**2.120**.

We can therefore conclude that the inclusion of a sulfur atom into the lactam ring has little effect on the molecules biological properties. Any substitution at the 3 position of the lactam ring decreases the potency of the molecule.

It should be noted that a large quantity of the salts of the lactams, the penultimate compound of type **2.103**, of each family subset have been kept and therefore a larger library of compounds (by the simple acylation reaction) is easily possible than that which has been made. A structure activity relationship could therefore be generated for these thialactam compounds.

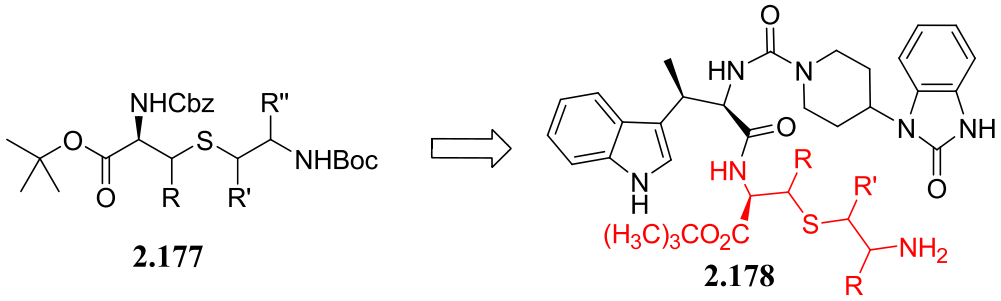
2.8 Conclusions and Future Work

We have shown that the syntheses of C-substituted γ-thialactams are possible *via* a modular approach starting from the simple amino acid cystine. These

compounds are a new class of GPCR ligand, showing BSCI activity comparable to their non-sulfur counterparts. Initial migratory data suggests that these lactams are inhibitors of leukocyte migration and comparable to the analogous BSCI lactams at μM concentrations, with decreased activity at the nM scale. The inclusion of sulfur into this class of lactam has little effect on its biological ability. Initial findings suggest that C-substitution at the 3-position of the 1,4-thiazepan-5-one class of lactam decreases their biological activity, and are less potent anti-inflammatory agents, with the exception of **2.118**. Further biological studies are needed in order to fully appreciate the effects of C-substitution on this class of compound. We envisage the synthesis of more C-substituted lactams *via* this modular approach and further biological studies in order to build a structure activity relationship for these classes of molecules.

The SSTR2 binding data shows that a chain length of at least eleven carbons is needed for inhibition of the binding of somatostatin at SSTR2 at 100 μM. Apart from the long chain dimethyl compounds, **2.106** and (**3*S*,6*R***)-**2.118**, the sulfur containing lactams show no displacement of somatostatin, though they do show leukocyte migratory inhibition, confirming it is not necessary for the compounds to occupy the somatostatin binding site to act as a potent BSCI.

The thialysine derivative and its analogues (**2.177**) prepared during the synthesis of these C-substituted γ-thialactams could be utilised by making new SSTR2 ligands (**Scheme 48**) by introducing this motif into SSTR2 ligands identified by Merck (see Section 1.4.1). Measuring the effect of these structural changes on the SSTR2 mediated activity of these compounds could then be calculated.



Scheme 48. Incorporating the thialysine derivatives to make new SSTR2 ligands. (see Section 1.4.1)

2.9 References

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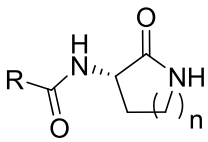
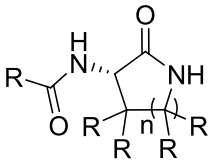
Chapter 3 – Asymmetric Lactams via Jocic-Reeve-Corey-Link Reactions

3.1 Introduction

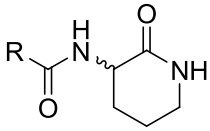
In continuation of our interest with previous BSCIs of type **3.1**-**3.3** with our aim of synthesising C-substituted lactams such as **3.4**-**3.6**, our attention turned to the synthesis of C-substituted δ-valerolactams, or piperidinones (**3.7**).



3.1-3.3

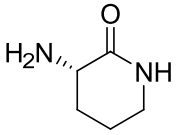


3.4-3.6

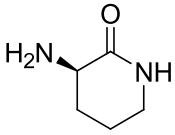


3.7

The simple 3-aminopiperidine-2-ones **3.8** and **3.9** are now commercially available and used as heterocyclic building blocks for the synthesis of a wide range of biologically important compounds, from conformationally constrained peptidomimetics, such as Freidinger lactams, to antileishmanials.[184-191]

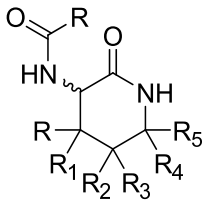


3.8



3.9

Although 3-aminopiperidine-2-ones are known, surprisingly and to the best of our knowledge only a few syntheses have been reported for C-substituted 3-aminopiperidine-2-ones (**3.10**).[189,192-205]

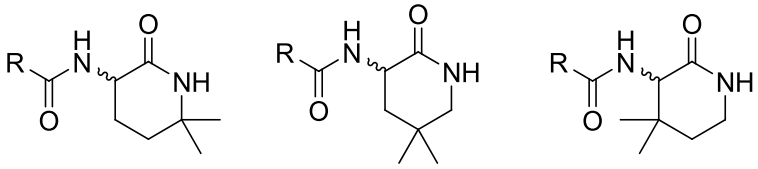


3.10

We have been interested in developing a short asymmetric synthesis of this type of lactam based on the following reasoning;

1. We know that 3-aminopiperidin-2-ones of type **3.7** inhibit leukocyte chemotaxis in vitro due to a range of chemokines and act as anti-inflammatory agents in vivo.[90,96-98]
2. The incorporation of substituents at the C-4,5 and 6 positions would not only introduce an additional point of diversity but also influence the conformation of the molecule.
3. An alternative asymmetric synthesis of substituted lactams could be attempted which, if successful, could be beneficial to the chemical community while simultaneously furthering our knowledge of BSCIs.
4. The chemistry used in synthesising this type of lactam could then be utilised in the synthesis of other substituted lactams or heterocycles, which may have important uses.

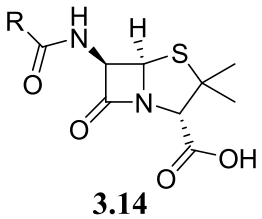
We began our endeavours by concentrating our efforts towards the synthesis of the dimethylpiperidin-2-ones (**3.11-13**).



3.11 **3.12** **3.13**

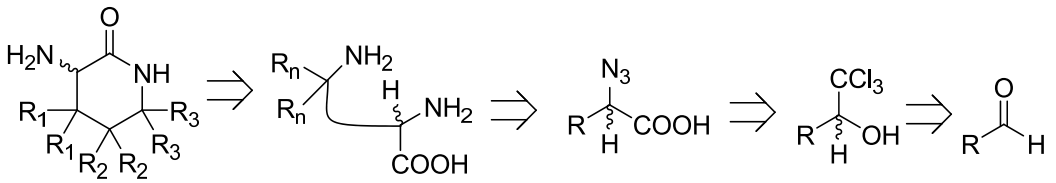
Dimethyl derivatives of lactams were of interest because our previous research had shown that related molecules of this type exhibited good biological activity. We also knew that α,α-disubstituted α-amino acids belong to the group of nonproteinogenic peptide components, that 2-aminoisobutyric acid derivatives make up a high proportion of natural polypeptide antibiotics and peptaibols, and although not directly related have structural similarities with the type of compounds we wished to synthesise.[206-209] The antibiotic penicillin[210-213] (**3.14**)

also has a gem-dimethyl structure with similarities to the compounds we wished to synthesise, further strengthening our reason for their synthesis.



3.14

We initially envisaged the dimethylpiperidin-2-one lactams (**3.15**) being formed by ring closure of a suitable enantiopure α-amino acid (**3.16**), which would be synthesised asymmetrically from the α-azido-acid (**3.17**) and the corresponding α-trichloromethyl carbinol (**3.18**), all derived from a suitable aldehyde (**3.19**) as shown in **Scheme 49**.



3.15 **3.16** **3.17** **3.18** **3.19**

Scheme 49. Proposed retrosynthetic route to substituted 3-aminopiperidine-2-ones

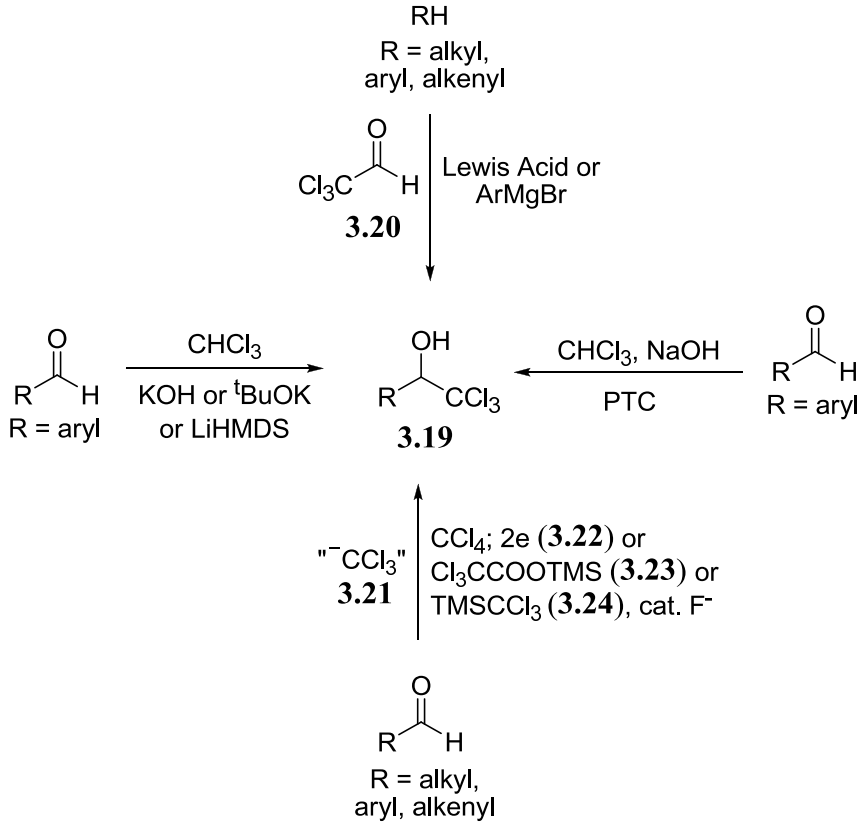
This process would involve a wide array of chemistry, some of which will briefly be discussed first.

3.2 α-Trichloromethyl Carbinol Chemistry

Throughout this and subsequent experiments our aim was to utilisie α-trichloromethyl carbinol derivatives (**3.19**), and their chemistry, in the synthesis of asymmetric lactams.

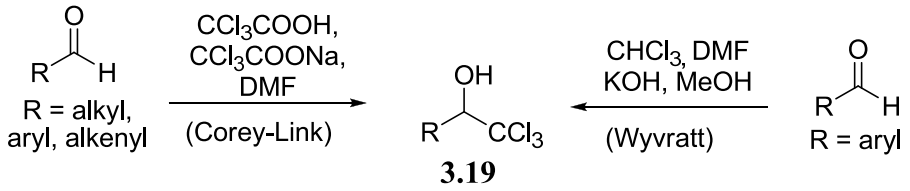
3.2.1 General Synthesis of α-Trichloromethyl Carbinols

The condensation of chloroform with aryl aldehydes and ketones under basic conditions are the earliest and most standard methods for the preparation of α-trichloromethyl carbinols.[214-219] Many different methods for their synthesis exist as summarised in **Scheme 50**. Chloral (**3.20**) is often used in the presence of a Lewis acid or arylmagnesium bromide with aromatic hydrocarbons to produce the desired α-trichloromethyl carbinol.[220-225] Of particular interest (*vide infra*) are the reactions of aldehydes with chloroform under basic conditions in the presence of phase transfer catalysts (PTCs) such as quaternary ammonium salts.[226-230] α-Trichloromethyl carbinols can also be synthesised by the reaction of electrophilic aldehydes with a trichloromethyl anion (**3.21**) generated *via* electrochemical reduction (**3.22**), or the reaction of trimethylsilyltrichloroacetate (**3.23**) or (trichloromethyl) trimethylsilane (**3.24**) with catalytic fluoride ion.[231-236]



Scheme 50. Synthetic routes to α-trichloromethyl carbinols.

All these methods to generate α-trichloromethyl carbinols have now been superseded by two main protocols, the Corey-Link and Wyvratt methods (**Scheme 51**).[215,237-239]

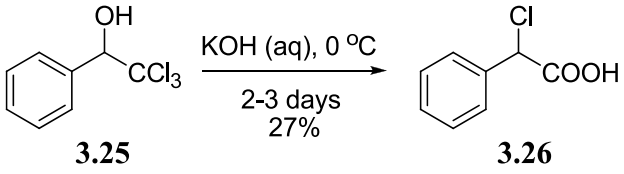


Scheme 51. Corey-Link and Wyvratt methods to the synthesis of α-trichloromethyl carbinols.

For our purposes, the preferred method for the synthesis of α-trichloromethyl carbinols is most certainly the Corey-Link method, as it provides rapid access to α-trichloromethyl carbinols from all classes of aldehydes without aldehyde enolisation. Although the Wyvratt method affords α-trichloromethyl carbinols with improved efficiency compared to the Corey-Link method, the basic nature of the method means that aliphatic aldehydes generate aldol products during the reaction, making it undesirable for our synthesis.[237]

3.2.2 Jocic Reaction

The Jocic reaction (**Scheme 52**), a reaction without precedent, was first reported by Jocic in 1897 and is the generation of α-chlorophenylacetic acid (**3.26**) from phenyltrichloromethylcarbinol (**3.25**) with ice cold aqueous potassium hydroxide.[240]



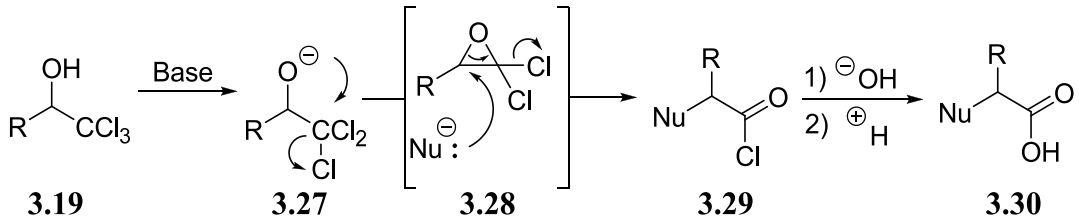
Scheme 52. Jocic Reaction.

With little to no subsequent work on this area until almost a century later, Reeves' seminal contribution both mechanistically and synthetically revived the reaction which subsequently gave rise to the reaction being named the Jocic-Reeve

reaction.[241-244] Notably, Reeve found that the Jocic reaction is general for secondary trichloromethyl carbinols and trichloroethanol, and that tertiary trichloromethyl carbinols form ketones with the loss of carbon monoxide.

3.2.3 Jocic-Reeve Reaction Mechanism

Jocic reported that his reaction proceeds through a *gem*-dichloroepoxide intermediate (**3.28**),[240] with later work by McElvain and Stevens,[245] and Weizmann[246] also claiming a reaction mechanism involving a *gem*-dichloroepoxide intermediate from α-trichloromethyl carbinols. The *gem*-dichloroepoxide intermediate was later verified by Reeve.



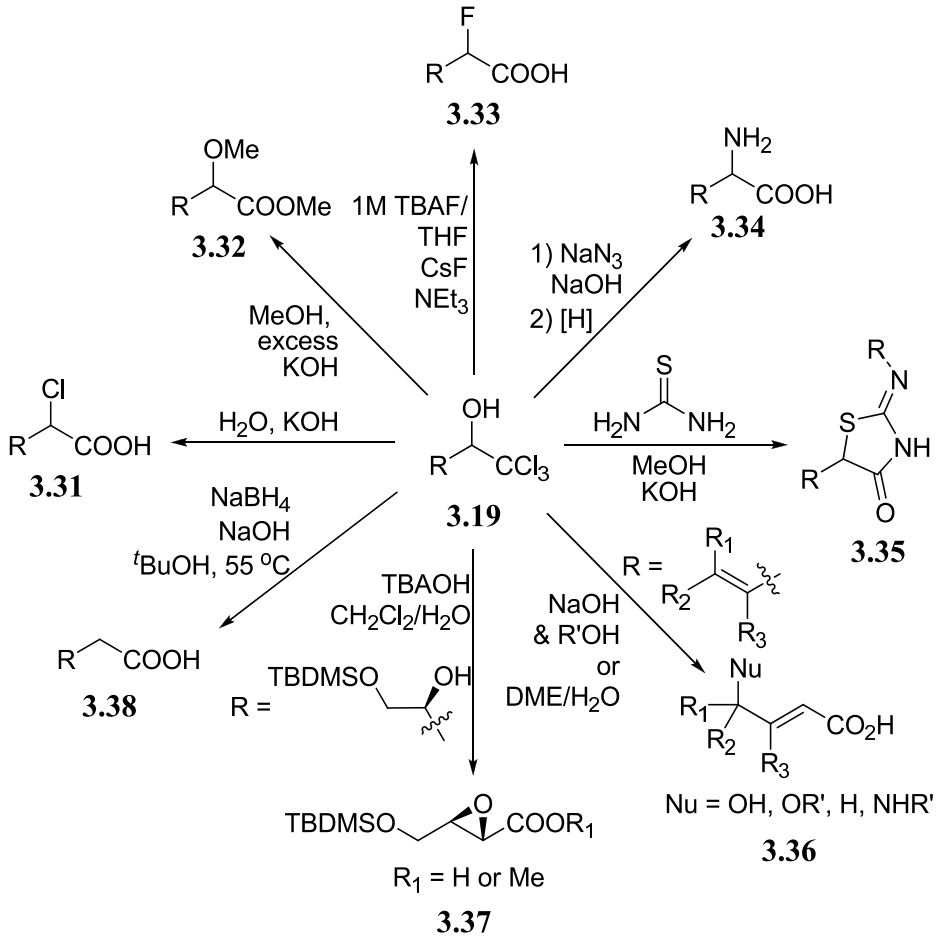
Scheme 53. The Jocic-Reeve reaction mechanism.

There has though been much speculation regarding the true mechanism of the Jocic reaction. Reeve performed detailed mechanistic investigations[241,243-244] and proposed four possible mechanisms including, a carbonium ion mechanism, a carbene mechanism, a hypochlorite mechanism and a chlorooxirene mechanism.[69-70,74] None of these truly accounted for all of the experimental observations, with the carbene mechanism the closer match. Reeve concluded that whilst the true mechanism of the Jocic reaction was uncertain the S_N2 mechanism represents a minor pathway while the major pathway involves either carbonium ion, carbene, hypochlorite or chlorooxirene intermediates.

3.2.4 Jocic-Reeve Reaction Uses

Since its re-emergence and popularisation the Jocic-Reeve reaction has been utilised in a number of synthetic applications (**Scheme 54**) with particular interest on the reactivity of α-trichloromethyl carbinols with a range of nucleophiles. As mentioned, α-chloroacids (**3.31**)[241] can be synthesised under the original conditions while MeOH acting as the nucleophilic source and an excess of KOH furnishes α-methoxyesters (**3.32**).[247] The reaction can be stopped at the α-methoxyacid stage if there is no excess hydroxide.[218,246,248] Other possible nucleophilic sources include fluoride from TBAF to generate α-fluoroacids (**3.33**),[249] sodium azide[250] and the subsequent reduction of the α-azidoacid to generate α-aminoacids (**3.34**)[251] and a variety of sulfur containing compounds such as thioureas, thiobenzhydrazide, *o*-aminothiophenol and thiosemicarbazide to generate a range of sulfur compounds,[242,252-257] such as thiazolidinones (**3.35**). More recently the Snowden group have extended the scope of the Jocic-Reeve reaction by investigating the regioselective substitution of *gem*-dichloroepoxides involving alkenyl trichlorocarbinols to give either γ-substituted enoic acids (**3.36**) or α-substituted acids, depending on the nature of the nucleophile in protic solvent.[258] They have also exploited the Jocic-Reeve reaction in the development of one-carbon homologation-functionalisation reactions, converting α-methyltrichlorocarbinols to their homologated carboxylic acids by treatment with either $NaBH_4$ in alkaline *tert*-butyl alcohol (**3.38**) or with sodium phenylseleno(triethyl)borate complex, prepared *in situ*, in ethanol.[259-260] Of significant importance to our studies, Oliver and Schmidt showed that the Jocic-Reeve reaction could be utilised to synthesise heterocycles when the substrate was tethered with an appropriately located nucleophile for intramolecular ring formation.[261] Indeed they reported that a vicinal hydroxyl group afforded stereospecific formation of chiral cis- and trans-epoxides (**3.37**) from the corresponding α-(trichloromethyl)glycols. Surprisingly, there are only a small

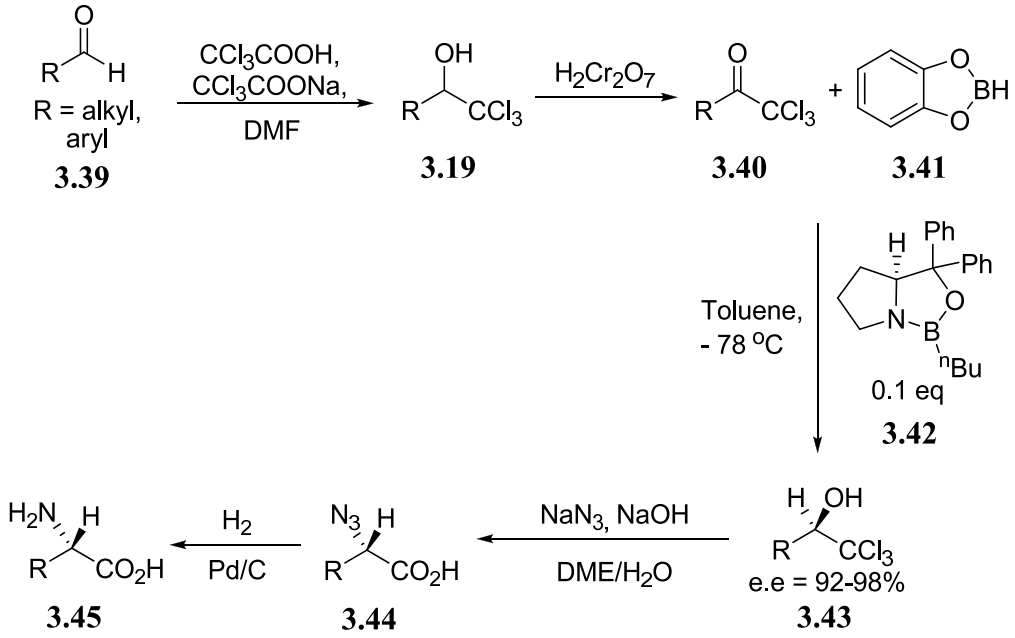
number of nucleophiles known (N_3^-, ArO^-, F^-) that give a stereoselective intermolecular Jocic-Reeve reaction.



Scheme 54. Reactions of α-trichloromethyl carbinols.

3.3 Corey-Link Chemistry

Arguably the most popular and recognisable utilisation of the Jocic-Reeve reaction, and one which certainly renewed interest in the area, is the Corey-Link reaction (**Scheme 55**).[237-238,262] It is a specific example of the much broader and more general Jocic-Reeve reaction but has somehow gained "named reaction" status through its popularity and third party classification.[260,263]



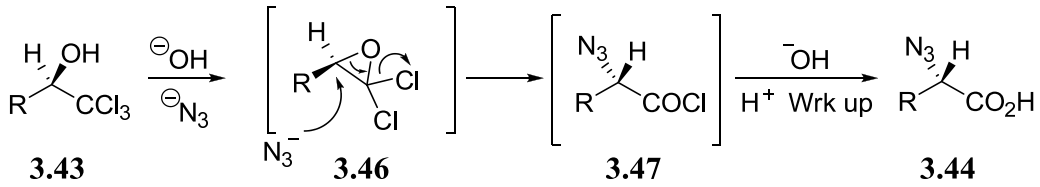
Scheme 55. Corey-Link reaction.

The Corey-Link reaction utilises asymmetric α-trichloromethyl carbinols (**3.43**) in the synthesis of non-proteogenic α-amino acids (**3.45**). Asymmetric α-trichloromethyl carbinols were prepared by the oxidation of achiral α-trichloromethyl carbinols (**3.19**) into trichloromethyl ketones (**3.40**) with chromium and the subsequent enantioselective reduction with the Corey-Bakshi-Shibata (CBS)[264] reduction catalyst (**3.42**). The trichloromethyl ketones were reduced either to the (*S*)- or the (*R*)-forms with greater than 96:4 enantioselectivity. A Jocic-Reeve reaction of the enantiopure α-trichloromethyl carbinols with sodium azide under basic conditions in a solution of dimethoxyethane (DME) and water gave enantiopure α-azidoacids (**3.44**) which were reduced with palladium catalysed hydrogenation to their respective α-amino acids in high yields and purity.[262]

3.3.1 Corey-Link Reaction Mechanism

The Corey-Link reaction is said to proceed *via* a *gem*-dichloroepoxide intermediate (**3.46**) followed by S_N2 attack of the azide nucleophile (**Scheme**

56).[262] The inversion of the stereochemistry is in agreement with earlier findings by Reeve, who incidentally was the first person to show that α-trichloromethyl carbinols could be transformed into α-amino acids,[251] albeit racemically, and indicative of the *gem*-dichloroepoxide intermediate.



3.43 **3.46** **3.47** **3.44**

Scheme 56. Corey-Link reaction mechanism.

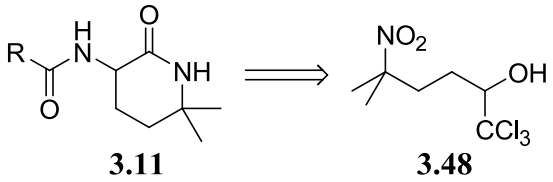
It is evident from the high yields and purity of the α-azidoacids, together with the complete inversion of stereochemistry, that the Corey-Link mechanism is a collapse of the Jocic-Reeve reaction mechanism to a major S_N2 type pathway due to the inclusion of the azide nucleophile. The Corey-Link synthesis shows that α-trichloromethyl carbinols are convenient precursors for the preparation of substituted carboxylic acids, esters, and other synthetically useful compounds.[260,265-267]

3.4 Dimethyl Lactam Derivatives *via* α-Trichloromethyl Carbinol Chemistry

As eluded to, we envisaged the dimethylpiperidin-2-one lactams (**3.15**) being formed by ring closure of a suitably substituted enantiopure α-amino acid (**3.16**) synthesised using the α-trichloromethyl carbinol chemistry described earlier.

3.4.1 Towards the Synthesis of Asymmetric 3-Amino-6,6-dimethylpiperidin-2-ones

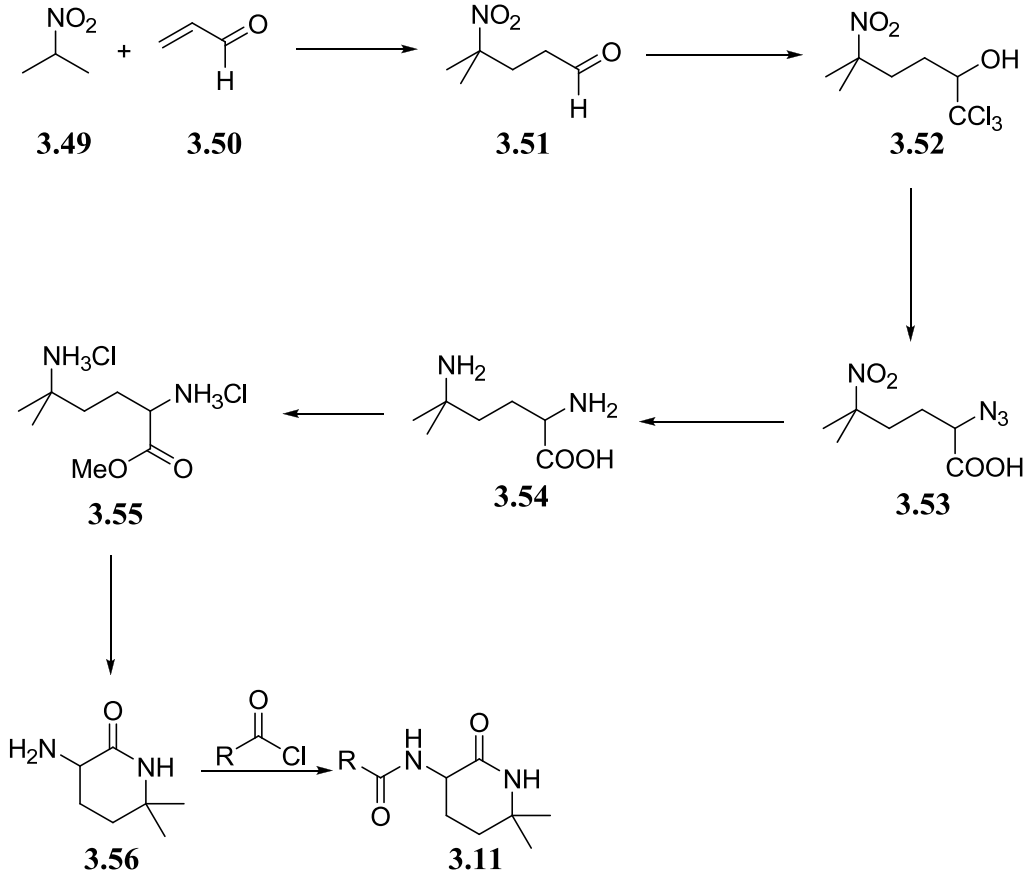
We envisaged the synthesis of the 3-amino-6,6-dimethylpiperidin-2-ones (**3.11**) via the δ-nitro-α-trichloromethylcarbinol (**3.48**).



3.11 **3.48**

Scheme 57. Retrosynthetic approach to 3-amino-6,6-dimethylpiperidin-2-ones.

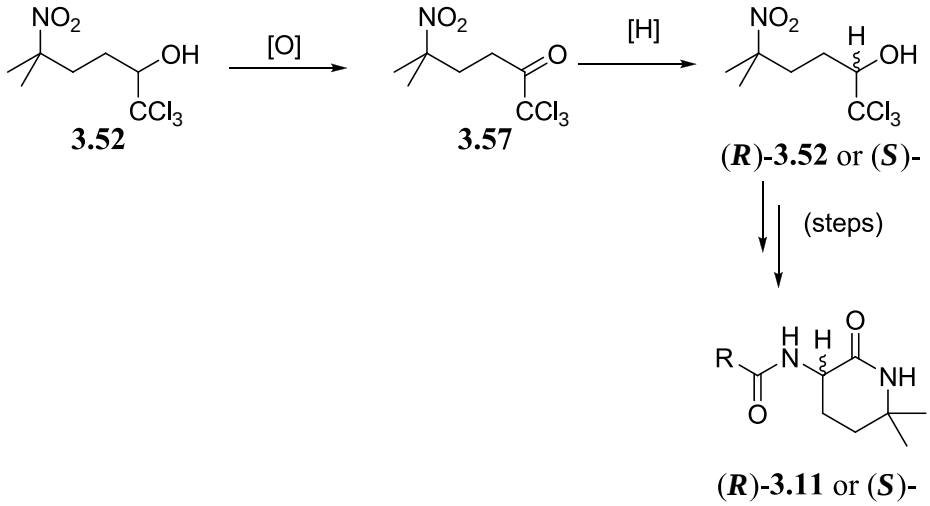
We hoped that conversion of this carbinol to the corresponding α-azidoacid (**3.53**), reduction and ring closure would furnish the desired product (**Scheme 58**).



3.49 **3.50** **3.51** **3.52** **3.53** **3.54** **3.55** **3.56** **3.11**

Scheme 58. Proposed route to 3-amino-6,6-dimethylpiperidin-2-ones.

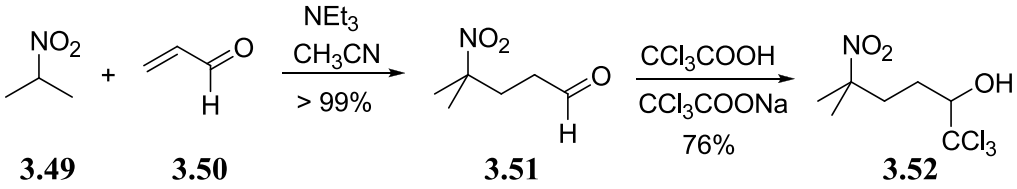
If the syntheses of the racemic piperidinones (**3.11**) were possible then Corey-Link chemistry would be used to synthesise the enantiopure piperidinones (**3.11**) by oxidising the δ-nitro-α-trichloromethylcarbinol substrate to its corresponding trichloromethyl ketone (**3.57**) and reducing using the CBS reduction, as in the Corey-Link reaction (**Scheme 59**).



Scheme 59. Proposed route to asymmetric piperidinones.

3.4.1.1 δ-Nitro-α-trichloromethylcarbinol Route

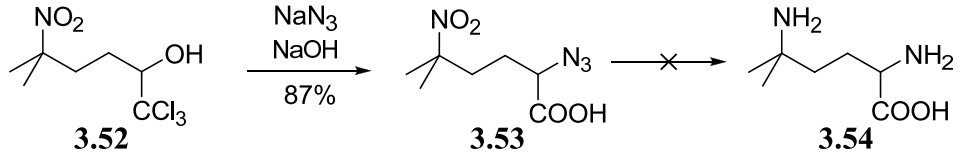
Synthesis of the δ-nitro-α-trichloromethylcarbinol was accomplished easily in high yield and purity over two steps. The Michael addition of 2-nitropropane (**3.49**) and acrolein (**3.50**) furnished the 4-methyl-4-nitropentanal (**3.51**) in quantitative yield.[268-274] The aldehyde then underwent the Corey-Link method for generating α-trichloromethylcarbinols using trichloroacetic acid and sodium trichloroacetate in DMF to give the desired racemic δ-nitro-α-trichloromethylcarbinol (**3.52**).



Scheme 60. Synthesis of δ-nitro-α-trichloromethylcarbinol.

DMF was preferred over DMSO[215,275] as the solvent as it gave better yields and reproducibility. Monitoring the reaction using NMR experiments in DMSO-d_6 gave inconsistent results. It is worth noting that the acrolein in the Michael addition needed to be distilled in order for the reaction to proceed.

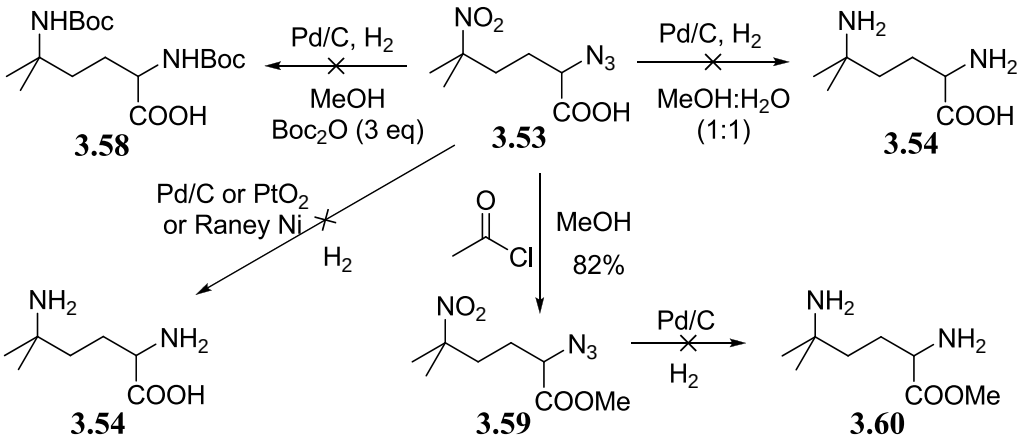
With the successful synthesis of the δ-nitro-α-trichloromethylcarbinol the proposed reaction scheme looked promising. Indeed, the Corey-Link reaction of the carbinol gave the desired 2-azido-5-methyl-5-nitrohexanoic acid (**3.53**) in high yields, but unfortunately the hydrogenation step to form the diamine (**3.54**), which would seem straight forward, could not be accomplished (**Scheme 61**).



3.52 **3.53** **3.54**

Scheme 61. Corey-Link chemistry and attempted synthesis of the diamine derivative.

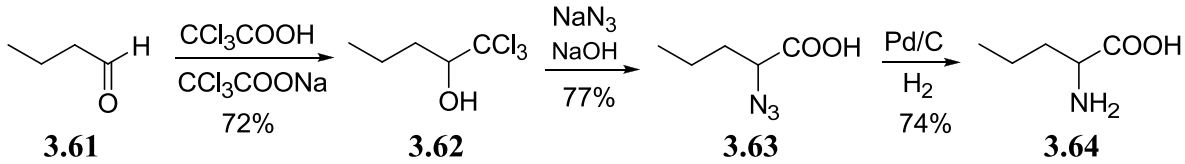
Many reducing agents were attempted (**Scheme 62**). Both Pd/C (the original Corey-Link method of preparing α-aminoacids) and PtO_2 catalysts with hydrogen were attempted, with little success. Even Raney nickel failed to reduce the carbinol to the α-aminoacid. It seemed logical to think that these reductions were failing because the diamine formed would be highly insoluble in the methanol solvent system employed in our hydrogenations, therefore a MeOH:H_2O (1:1) mixture was attempted again with little luck. The same train of thought led to the attempted Boc protection *in situ* of the product by using an excess of di-*tert*-butyl dicarbonate (**3.58**), this also failed. The α-azidoacid was methylated (**3.59**) using acetyl chloride-methanol as a final attempt at hydrogenating the resulting ester to a useful diamine as we wanted to eliminate the possibility of the acid affecting the reduction. Again I could not isolate the desired product from the reaction. Unfortunately I found that it is much more difficult to perform a hydrogenation on a compound that contains acid, azide and nitro functionalities than originally anticipated, and I was unable to synthesise or isolate a useful diamine derivative.



Scheme 62. Reduction attempts on the nitro-azido-acid (**3.53**).

3.4.1.2 Reduction Test

Due to the problems with the hydrogenation, and to check that it wasn't our method that was affecting our results, I decided to quickly investigate a similar type chain acid-azide to see if we could produce the desired α-aminoacid (**Scheme 63**). The Fox lab had plenty of butyraldehyde (**3.61**) and the Corey-Link chemistry carried out on that aldehyde indeed furnished the desired α-aminoacid (**3.64**). I at least felt assured that the method of performing hydrogenations was adequate and that my concerns that a compound containing acid, azide and nitro functionalities was difficult to reduce confirmed.

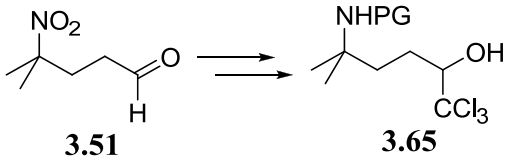


Scheme 63. Testing of Corey-Link chemistry with butyraldehyde (**3.61**).

3.4.1.3 δ-Amino-α-trichloromethylcarbinol Route

The unsuccessful route to the *gem*-dimethyl lactams *via* the δ-nitro-α-trichloromethylcarbinol was a disappointing result and it became apparent that if I wanted to continue our syntheses of the lactams *via* Jocic-Reeve-Corey-Link chemistries we needed to synthesise an α-trichloromethylcarbinol substrate which contained a protected δ-amino group (**Scheme 64**). I set out to synthesise our new carbinol substrate (**3.65**) by performing the necessary chemistry on our previously

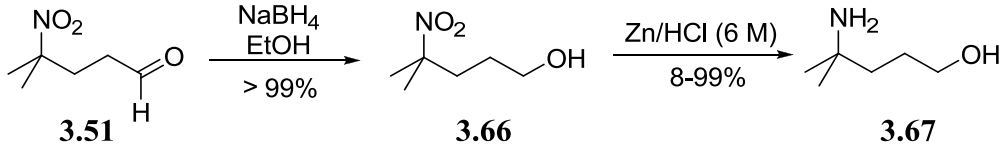
synthesized 4-methyl-4-nitropentanal (**3.51**) and attempting to reduce the nitro functional group of this substrate first before undergoing the Jocic-Reeve type reaction.



3.51 **3.65**

Scheme 64. Alternative substrate for the synthesis of the desired piperidinones.

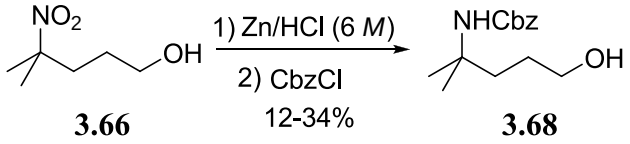
Reduction of the nitro group was attempted from various analogues of the nitro aldehyde (**3.51**). Direct reduction of the nitro group with H_2 and Pd/C to generate the reduced amino aldehyde seemed unlikely, and indeed did not work. Reduction of the aldehyde with sodium borohydride in ethanol furnished the nitro alcohol (**3.66**) in quantitative yields on small and large scale. The reduction of the nitro group from this compound *via* H_2 and Pd/C was again unsuccessful, but a method used by Jim Andersons group in reducing tertiary nitro compounds using zinc and 6M HCl gave the corresponding amino alcohol (**3.67**, **Scheme 65**).[276-280]



3.51 **3.66** **3.67**

Scheme 65. Reduction of 4-methyl-4-nitropentanal.

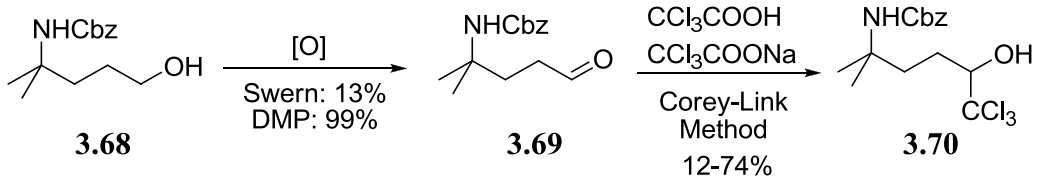
Although the reduction of the nitro compound (**3.66**) succeeded using zinc, isolating the reduced product (**3.67**) gave unreliable and poor yields, typically between 8-14% (with the exception of 99% on one ocassion). Protection of the amine group from this isolated product is possible but also unreliable. It was found that protecting the amine directly after taking up the reaction in base (**Scheme 66**) produced the desired protected amino alcohol derivative (**3.68**) reliably in overall yields of between 12-34%. We also generated the Boc protected version of the protected amino alcohol (**3.67-Boc**) in yields of up to 55%.



3.66 **3.68**

Scheme 66. Generating the protected amino alcohol **3.68**.

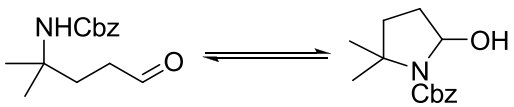
With the successful synthesis of the protected amino alcohol we could now oxidize this compound and perform the required Jocic-Reeve-Corey-Link chemistry. Oxidation of **3.68** was achieved in high yields if Dess-Martin periodinane (DMP)[281-284] was used, while the Swern oxidation[285-287] gave poor results (**Scheme 67**). The Corey-Link method of synthesising α-trichloromethyl carbinols was utilised to synthesise the desired carbinol (**3.70**) from its aldehyde (**3.69**).



3.68 **3.69** **3.70**

Scheme 67. Synthesis of the amine-protected trichlorocarbinol.

Several interesting points should be noted. We could not understand why the Swern oxidation gave poor results, and when we initially used DMP for the oxidation we were generating a compound which gave experimental data that was inconsistent with the expected structure of **3.69**. We later found that the aldehyde is most likely in equilibrium with, or converted to, its pyrrolidine form (**Scheme 68**). As we would later find, aldehydes of this type, even though Cbz-protected, could form cyclic compounds, or react to produce undesirable products.

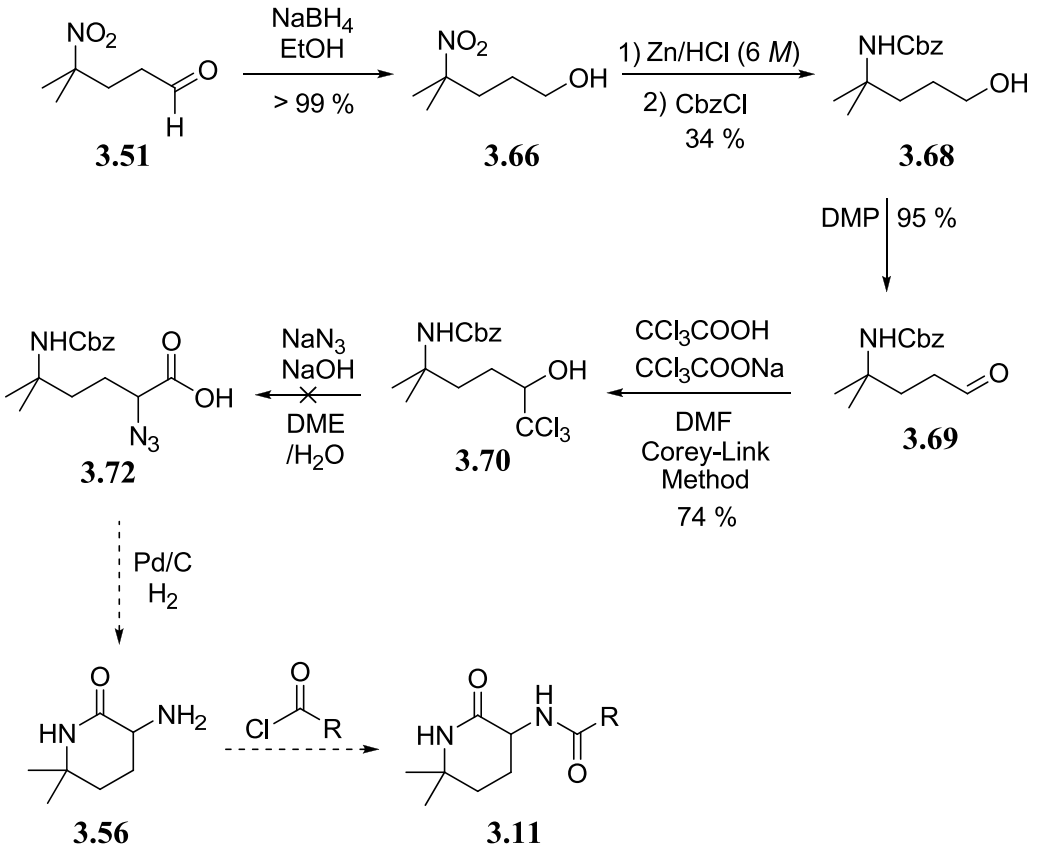


3.69 **3.71**

Scheme 68. Compound **3.69** in equilibrium with **3.71**.

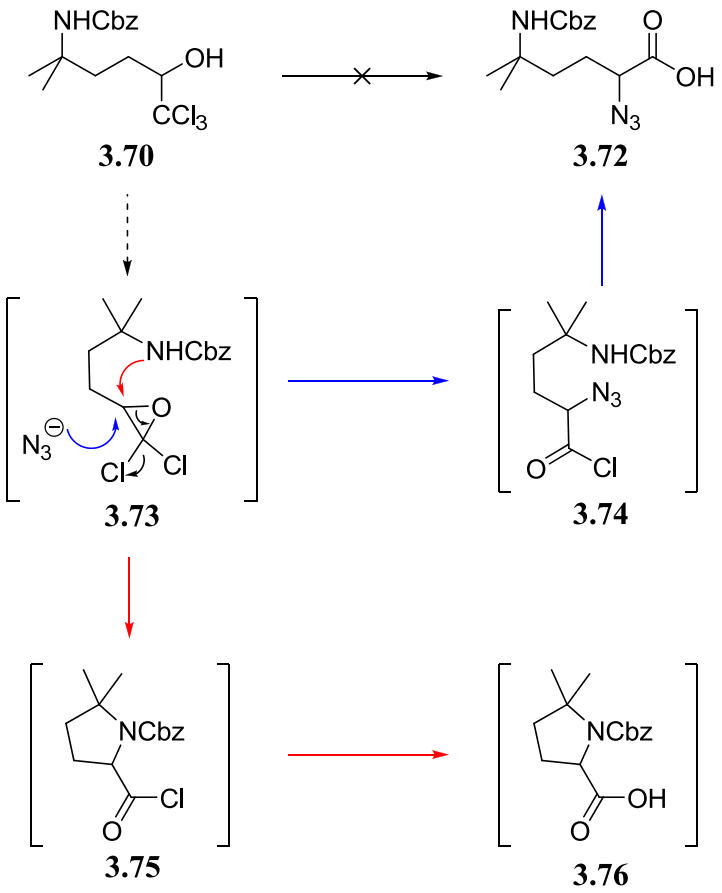
In either case, when the Corey-Link method was applied to isolated product **3.69** the desired α-trichloromethyl carbinol was generated. With the synthesis of the

protected δ-amino-α-trichloromethyl carbinol (**3.70**), we envisioned conversion to the desired 3-amino-6,6-dimethylpiperidin-2-ones (**3.11**) by performing the required Corey-Link chemistry (**Scheme 69)**.



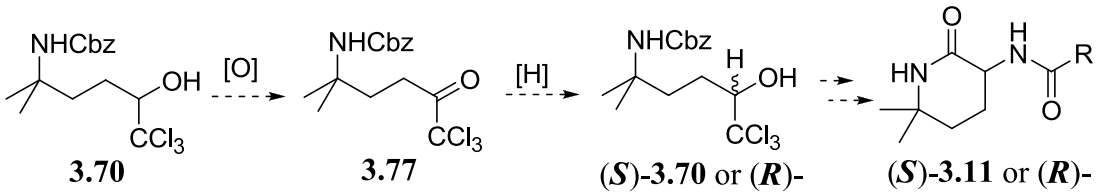
Scheme 69. Synthesis of 3-amino-6,6-dimethylpiperidin-2-ones.

While several substrates have been utilised in the Corey-Link process (*vide supra*), amine-containing substrates have rarely been studied. Treatment of the trichloromethyl carbinol (**3.70**) was expected to provide α-dichloroepoxide intermediate (**3.73**) as previously proposed for this process which, upon epoxide cleavage by azide with inversion, would provide acid chloride (**3.74**) which would then furnish the azido-acid (**3.72**) upon work-up (**Scheme 70**). However, despite extensive experimentation, this strategy was unsuccessful. It is thought that the amine plays a role in an unexpected capture of the presumed dichloroepoxide intermediate (**3.73**) which generates an undesired pyrrolidine product (**3.76**), but this was never isolated from the crude reaction mixture.



Scheme 70. Attempted Corey-Link chemistry on the protected δ-amino α-trichloromethyl carbinol (**3.70**).

We initially foresaw the use of chromium for the oxidation of carbinols to the trichloroketones and CBS catalyst for the asymmetric reductions (*i.e.* Corey-Link reaction in **Scheme 71**) but simultaneous work carried out on the use of CCl_3 as a directing group for asymmetric transfer hydrogenation meant the CBS catalyst was abandoned in favour of ruthenium-based catalysts. In any case, we were unable to oxidise the α-methyl trichlorocarbinol (**3.70**) to its trichloroketone (**3.77**) counterpart using DMP, IBX, chromium or Swern oxidations. Combined with the failure of the Corey-Link procedure to form the azido-acid (**3.72**) the syntheses of these types of compounds were abandoned.

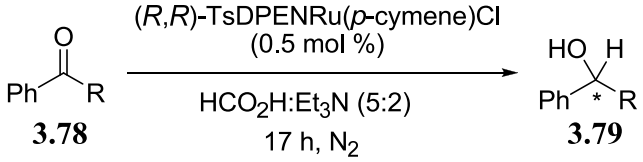


3.70 **3.77** (***S***)-**3.70** or (***R***)- (***S***)-**3.11** or (***R***)-

Scheme 71. Asymmetric synthesis of piperidinones.

3.4.1.4 Asymmetric Transfer Hydrogenation of Trichloroketones

Investigations into asymmetric transfer hydrogenations[288-290] of chloroketones and subsequently trichloroketones (**3.78**) were being carried out within our group by Michael Perryman. He found that ruthenium could be used for the asymmetric transfer hydrogenation of chloroketones (**Figure 18**).



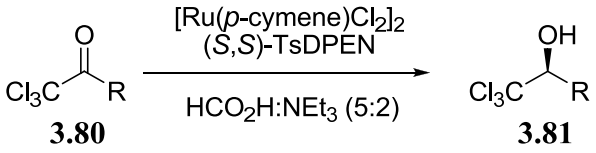
3.78 **3.79**

R	***Conversion (%)***	***ee (%)***
CH_3	> 99	95
CH_2Cl	> 99	79
$CHCl_2$	> 99	71
CCl_3	> 99	35

Figure 18. Asymmetric transfer hydrogenation of chloroketones using ruthenium catalyst.

Results for aromatic trichloroketones, producing the corresponding asymmetric trichlorocarbinol, did not look promising, giving low enantiomeric excesses. Undeterred, Perryman investigated the use of ruthenium as a catalyst for a range of aliphatic trichloroketones. These trichloroketones (**3.80**), synthesised from their respective aldehydes, were subjected to asymmetric transfer hydrogenations to give asymmetric α-trichloromethyl carbinols (**3.81**) in high yields and enantiomeric excesses. The best results obtained, some of which are shown in **Figure 19**, used TsDPEN and [Ru(*p*-cymene)Cl_2] dimer to generate the transfer catalyst TsDPENRu(*p*-cymene)Cl.

Preliminary results, again by Perryman, show that alkyl side chains of trichloroketones can be reduced to their respective α-trichloromethyl carbinols in high yields and enantiopurity using ruthenium catalysts, therefore allowing us to use this chemistry for the generation of asymmetric lactams within our synthesis.

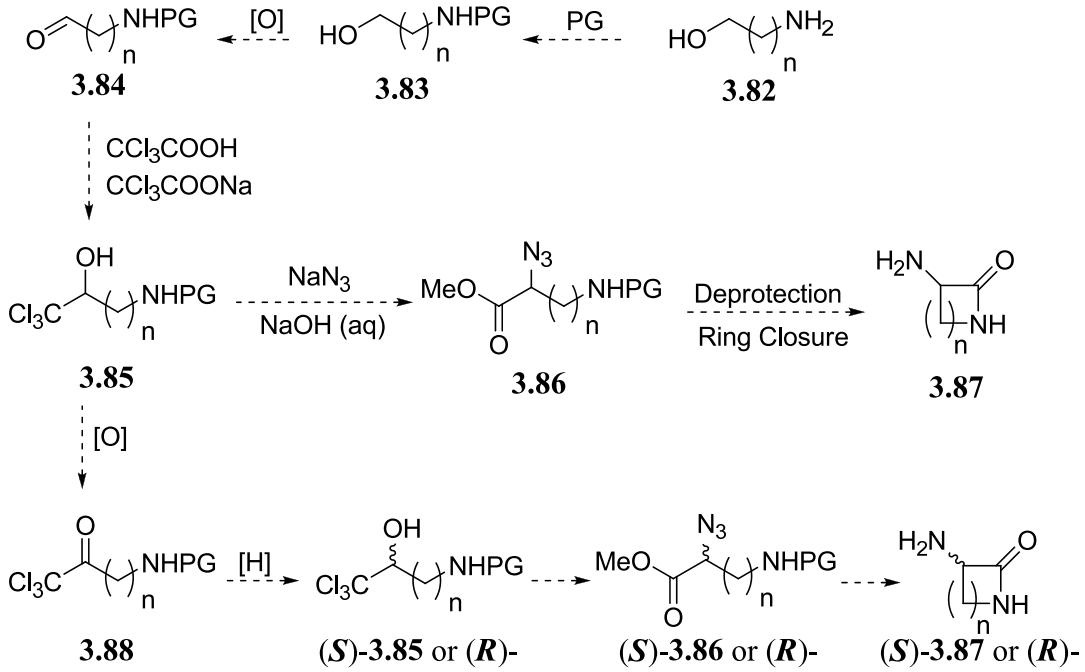


R	*Conversion (%)*	*Yield (%)*	*ee (%)*
Me	> 95	50	99
^{n}Pr	> 95	37	95
$(CH_2)_9CH_3$	> 95	95	95
$(CH_2)_2Ph$	> 95	90	97
$CH(CH_3)(CH_2)_2CH_3$	> 95	68	91:89 (4:3)

Figure 19. Selected results for the asymmetric transfer hydrogenation of aliphatic trichloroketones.

3.5 Towards a General Synthesis of Asymmetric Lactams

During the unsuccessful attempts at synthesising the dimethylpiperidinones I was also attempting to perform the general synthesis of 3-amino-lactams from simple amino-alcohols (**Scheme 72**). Again I would utilise the Jocic-Reeve-Corey-Link reaction for the synthesis of racemic lactams and, if successful, the asymmetric transfer hydrogenations using ruthenium chemistry to generate the asymmetric lactams. This would allow the synthesis of C-substituted lactams from substituted amino-alcohols.

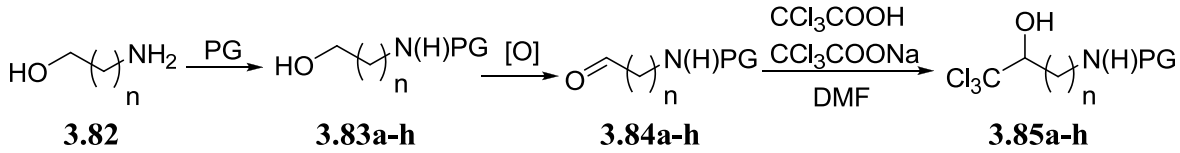


Scheme 72. Proposed general synthetic route to lactams.

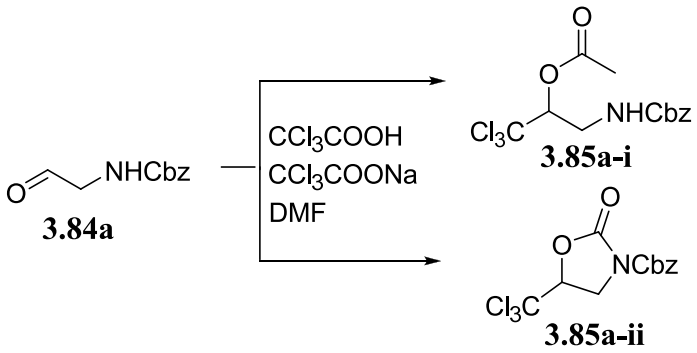
To begin with I used benzyl chloroformate as the protecting group (much like the piperidinone strategy) as I was hoping that the amino lactams would be formed by simultaneously deprotecting, reducing and cyclising the azido acid (**3.86**) formed from the Corey-Link reaction. Unfortunately a number of problems arose when attempting the synthesis of these lactams with the Cbz protecting group. When ethanolamine was used (n=1), the acetate (**3.85a-i**) or oxazolidinone (**3.85a-ii**) of the methyltrichlorocarbinol was formed during the Corey-Link method. The synthesis from propanolamine (n=2) works up to the α-methyl trichlorocarbinol, albeit with very low yields (16%), but the azido acid could not be generated. For the pentanolamine derivative (n=4) a cyclised product of unknown structure is formed. The difficulty and unreliability in synthesising the Cbz-protected methyltrichlorocarbinols was apparent. Despite the amine group being protected, it still plays a role in disrupting our chemistry. This finding simultaneously became apparent during the synthesis of these and our piperidinones (*vide supra*) and so the use of phthalidimides was rationalised in order to generate the trichlorocarbinols without the interference of the amine during the reactions. If the synthesis of lactams using phthalimides was realised at least the piperidinones could again be attempted. Indeed it is easily possible to synthesise the full set of phthalimide protected trichlorocarbinols (**3.85a-h**) in good yields (**Figure 20**).

Complications became apparent when attempting the Corey-Link reaction with NaOH and NaN_3 on the phthalimide protected trichlorocarbinol substrates (**3.85e-h**). The basic nature of the Corey-Link reaction was not compatible with the phthalimide protecting group. Indeed there are a number of possible reaction pathways that can occur during these reactions. A modification of the Corey-Link procedure where DBU was used instead of hydroxide in MeOH seems an attractive alternative,[263] but it has been shown that this procedure is only successful with tertiary trichloromethyl alcohols. The reason for the poor

performance of secondary trichloromethyl carbinols under these conditions is unknown. Although our scheme looks attractive for the general synthesis of lactams, we have not yet been successful in synthesising compatible protected amino trichloromethyl carbinols with the Jocic-Reeve-Corey-Link chemistries.



3.82 **3.83a-h** **3.84a-h** **3.85a-h**



PG = Cbz			PG = Phth		
(X)	***n***	***Yield (%)***	***(X)***	***n***	***Yield (%)***
3.83a	1	53	**3.83e**	1	48
3.83b	2	99	**3.83f**	2	35
3.83c	3	82	**3.83g**	3	NA
3.83d	4	71	**3.83h**	4	68
3.84a	1	45	**3.84e**	1	66
3.84b	2	10	**3.84f**	2	65
3.84c	3	94	**3.84g**	3	NA
3.84d	4	78	**3.84h**	4	77
3.85a	1	NA[#]	**3.85e**	1	43
3.85b	2	16	**3.85f**	2	76
3.85c	3	NA	**3.85g**	3	NA
3.85d	4	NA[*]	**3.85h**	4	44

Figure 20. Synthesis of alkylamine-protected trichloromethylcarbinols.[#]Product formed was the trichloroacetate (**3.85a-i**) or oxazolidinone (**3.85a-ii**) on separate occasions. *Unknown cyclised product formed from the reaction. NA = not attempted.

3.6 Conclusions

Efforts have been made to the synthesis of substituted piperidinones, as well as employing Jocic-Reeve-Corey-Link chemistry to the general synthesis of lactams, ultimately looking to the synthesis of C-substituted lactams. Protected amino trichloromethyl carbinols are much harder to work with than previously

anticipated. The use of a phthalimide protecting group may provide the answer for utilising trichloromethyl carbinol chemistry in the presence of an amine group, if a successful modified Corey-Link procedure is found. A method for asymmetric transfer hydrogenation of trichloroketones has been established and can be utilised in the synthesis of asymmetric lactams if/when a route has been established.

3.8 References

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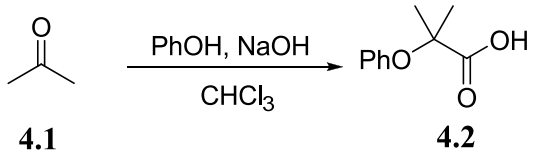
CHAPTER 4 – Asymmetric Substituted β-Hetero-δ-Lactams via Hybrid-Bargellini Reactions

4.1 Introduction

Continuing our interest in the field of substituted lactams, trichloromethyl carbinol reactions and using the chemistries we had developed within the group, our attention turned to substituted enatiomerically enriched heterocycles, more specifically substituted β-hetero-δ-lactams.

4.2 Bargellini Reaction

The Bargellini Reaction is a multicomponent coupling reaction which also involves *gem*-dichloroepoxides.[291] First reported in 1906, it involves the *in situ*-generation of trichloromethide anion from chloroform in the presence of NaOH and its reaction with phenol and acetone to generate α-phenoxyisobutyric acid (**Scheme 73**).[292]

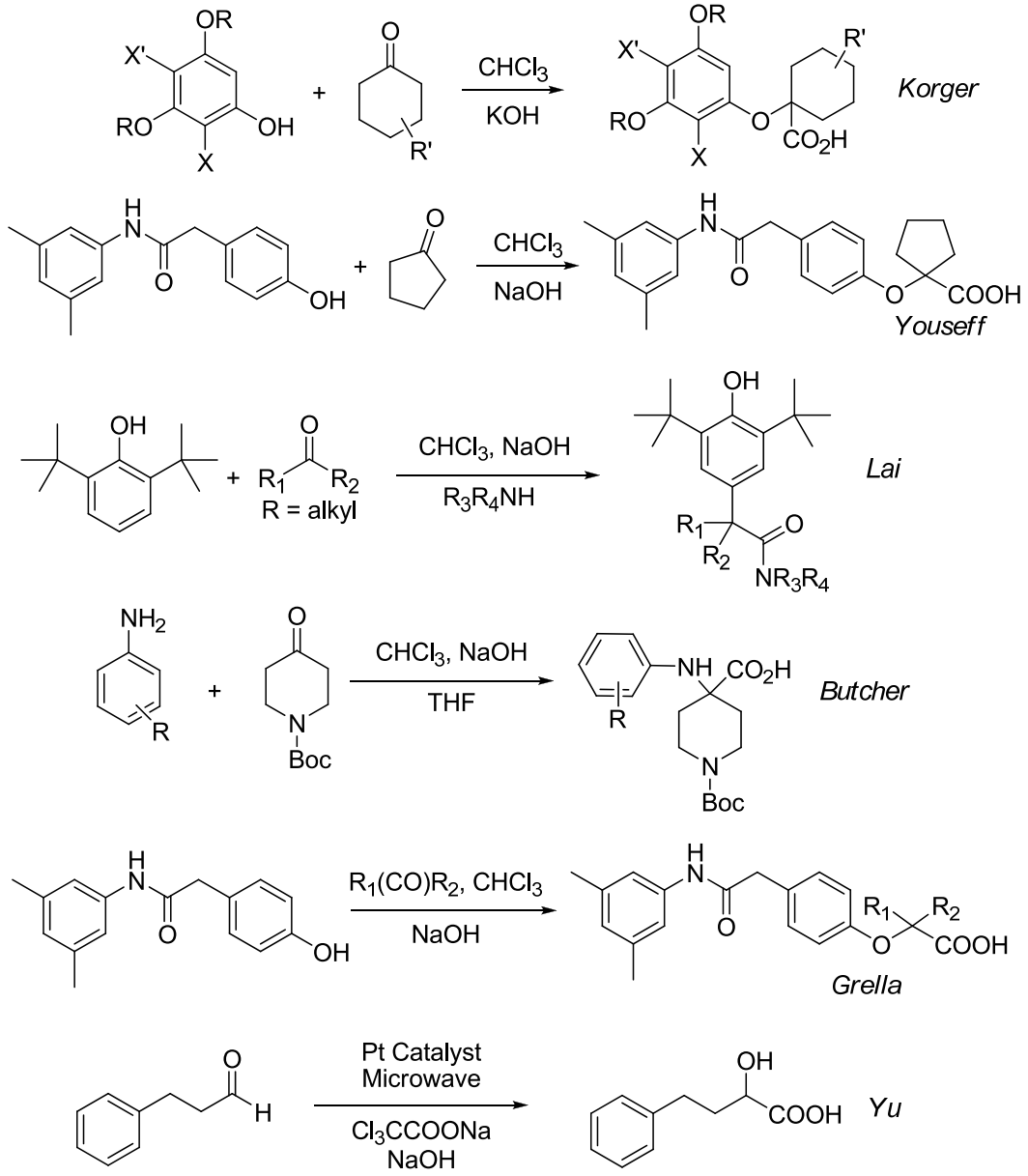


4.1 **4.2**

Scheme 73. The Bargellini Reaction.

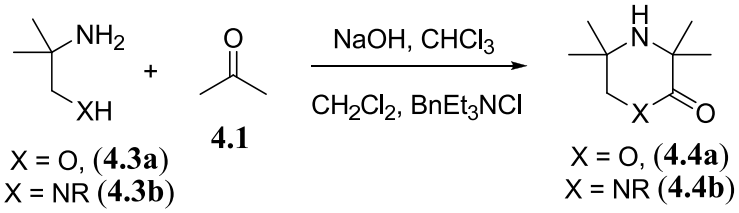
Since its initial report, the Bargellini reaction has been extensively investigated with many advances coming from research groups within the pharmaceutical industry. Variants of both nucleophile and ketone have been investigated; Korger reported the use of substituted phenols as nucleophiles to prepare griseofulvin analogues;[293] Youseff used phenols as nucleophiles and cyclopentanone as the ketone;[294] Lai used hindered amines as nucleophiles to create a series of hindered

morpholinones and piperazinones,[295-298] and more recently activated arenes as nucleophiles to give hindered phenols;[299] Butcher[300] used aromatic amines as nucleophiles; Grella investigated a wide range of cyclic ketones;[301] while Yu used Bargellini reactions to generate α-hydroxy acids,[302] as summarised below in **Scheme 74.**



Scheme 74. Bargellini reactions using variants of both nucleophile and ketone.

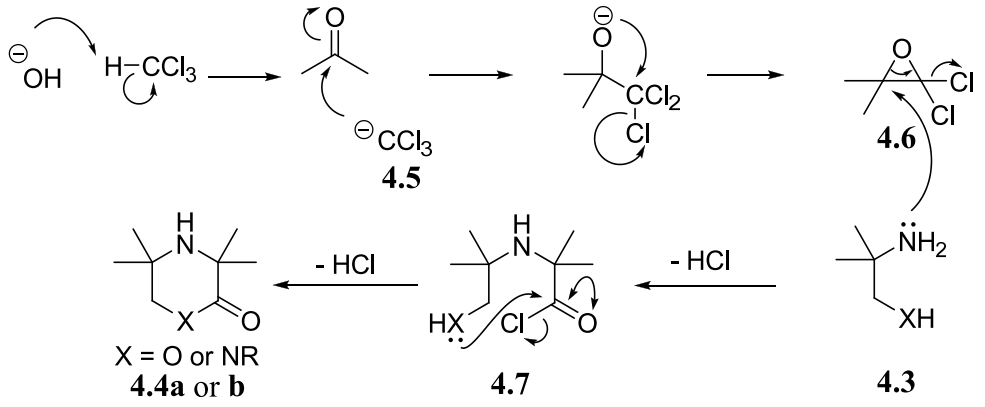
Of importance to our research was the work carried out with binucleophiles in the Bargellini reaction, in particular the synthesis of hindered morpholinones or piperazinones (**4.4**) from ketones (such as acetone) and 2-amino-2-methyl-1-propanol or 1,2-diaminopropanes (**4.3**), **Scheme 75**. Work performed by Lai (*vide supra*) of the BF Goodrich Corporation, who has been active in this area of chemistry over the past three decades, is of particular interest.



Scheme 75. Heterocycles *via* the Bargellini reaction.

4.2.1 Mechanism of Bargellini Reaction

During the Bargellini reaction the product is formed by regioselective addition to an intermediate *gem*-dichloroepoxide (**4.6**). Typically the intermediate is formed by base deprotonation of chloroform with the *in-situ*-generated trichloromethide anion (**4.5**) coupling to a sterically accessible ketone (**Scheme 76**). The reaction of a nucleophile with the *gem*-dichloroepoxide then follows, in the same manner as the Jocic-Reeve-Corey-Link reactions (*vide supra*). If the nucleophile is a tethered binucleophile (as in **Scheme 76**) then the acyl chloride generated can be captured by the tethered nucleophile to form a heterocyclic compound.



Scheme 76. Mechanism of the Bargellini reaction.

Worth noting are the statements by Snowden, who is an expert in the field of Jocic-Reeve-Corey-Link-Bargellini reactions, who has said regarding the Bargellini reaction "*in general, alkyl aldehydes are not compatible with the reaction primarily due to competing aldol condensation and the relatively slow rate of dichloroepoxide formation from any formed secondary trichloromethyl alkoxide*".[260]

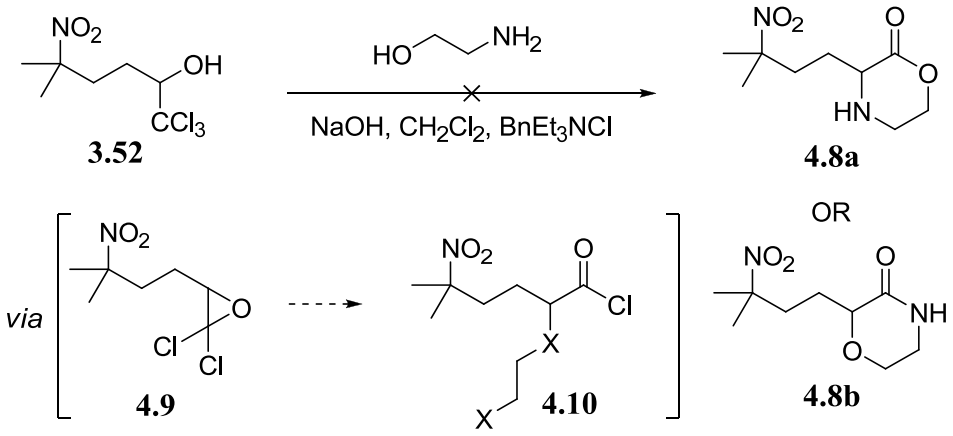
4.3 Heterocycles *via* Hybrid-Bargellini Reactions

As a continuation of our work towards substituted chiral lactams, we hoped to utilise some of the α-trichloromethyl carbinols we had previously synthesised in a hybrid-Bargellini type reaction.

4.3.1 Utilising Previous Compounds

Our first attempted synthesis of a heterocycle was *via* the δ-nitro-α-trichloromethylcarbinol (**3.52**) previously synthesised. We hoped that the carbinol would form the *gem*-dichloroepoxide intermediate (**4.9**) with the use of NaOH, followed by the reaction of our binucleophile, ethanolamine, with this

intermediate with ring closure occuring by trapping of the acid chloride (**Scheme 77**). The same conditions were used as those for the Bargellini reaction in Lai's work, but unfortunately we were unable to isolate the desired product. Although we were confident that cyclisation did occur during these reactions (due to the appearance of multiple stereocentre peaks in the NMR), we were less confident about the suitability of the nitro carbinol for these reactions.



Scheme 77. First attempt at a hybrid-Bargellini reaction utilising 3.52.

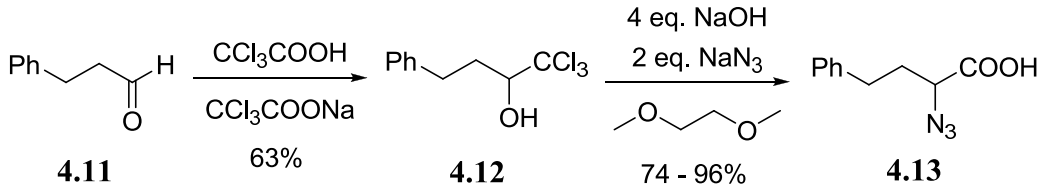
Other previously synthesised trichloromethyl carbinols (*vide supra*) were also attempted giving inconclusive results.

4.3.2 Checking the Chemistry – Modified Corey-Link Reaction

At this juncture we were concerned with the selection of our substrate and whether or not we could use a binucleophile with alkyl trichloromethyl carbinols. We therefore focused our attention on checking the chemistry with the Corey-Link reaction and to see whether or not we could trap the proposed dichloroepoxide intermediate during the reaction with two nucleophiles.

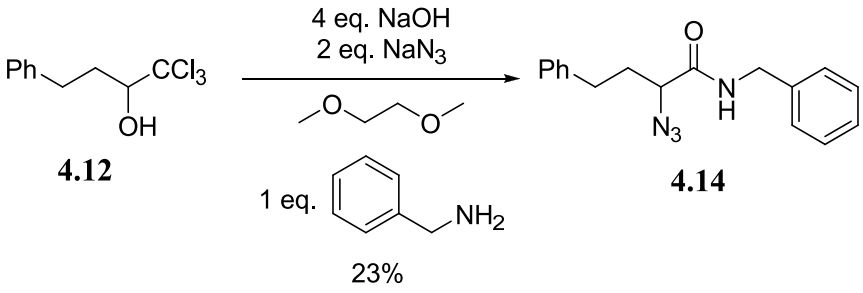
We used hydrocinnamaldahyde (**4.11**) as our candidate molecule because it was structurally similar to the substrates we intended to use – it contains a bulky

quaternary carbon three carbon units away from the reactive site, separated by two CH_2 units. Corey-Link chemistry on this substrate furnished the corresponding 1,1,1-trichloro-4-phenylbutan-2-ol (**4.12**) and its azido-acid (**4.13**) in good to excellent yields (**Scheme 78**).



Scheme 78. Corey-Link reaction using hydrocinnamaldehyde.

When we introduce a second nucleophile into the Corey-Link reaction (in this case one equivalent of benzylamine) we were very pleased to discover that we could indeed trap the acid chloride intermediate to form the α-azido amide (**4.14**) in reasonable yields (**Scheme 79)**.

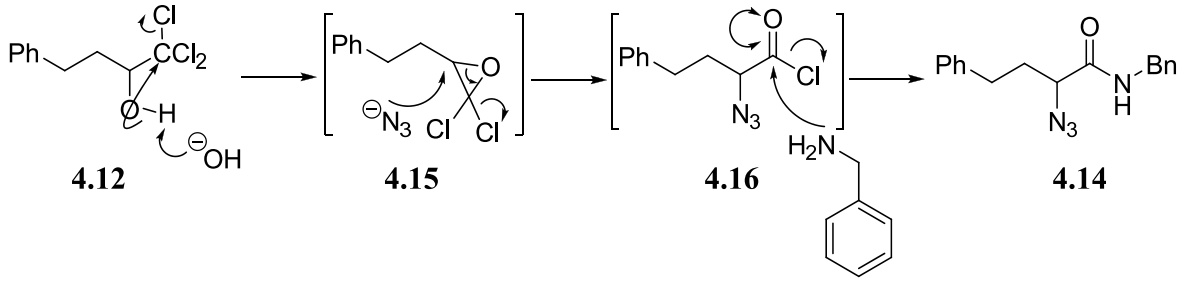


Scheme 79. Modified Corey-Link reaction using two nucleophilic sources.

This is the first known example of utilising the Corey-Link reaction with two competing nucleophiles and generating an α-azido amide using an α-trichloromethyl carbinol. This at least confirmed our belief that we could trap the acid chloride intermediate formed during the reaction of an alkyl trichlomethyl carbinol.

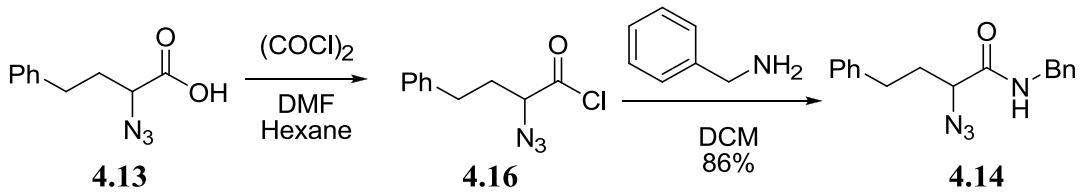
In line with previous examples of this type of chemistry we propose the reaction mechanism in **Scheme 80** and believe the mechanism to proceed *via* a *gem*-

dichloroepoxide intermediate (**4.15**) with the competing benzylamine nucleophile trapping the α-azido acid chloride intermediate (**4.16**).



Scheme 80. Proposed mechanism of our modified Corey-Link reaction with two competing nucleophiles.

To confirm the structure of our α-azido amide and our findings we also synthesised **4.14** stepwise (**Scheme 81**) from the α-azido acid Corey-Link adduct (**4.13**) by converting this acid into the acid chloride (**4.16**) and coupling with benzylamine. We have no doubt that the compound we synthesised is indeed the α-azido amide (**4.14**) with all characterisation data supporting this structure.

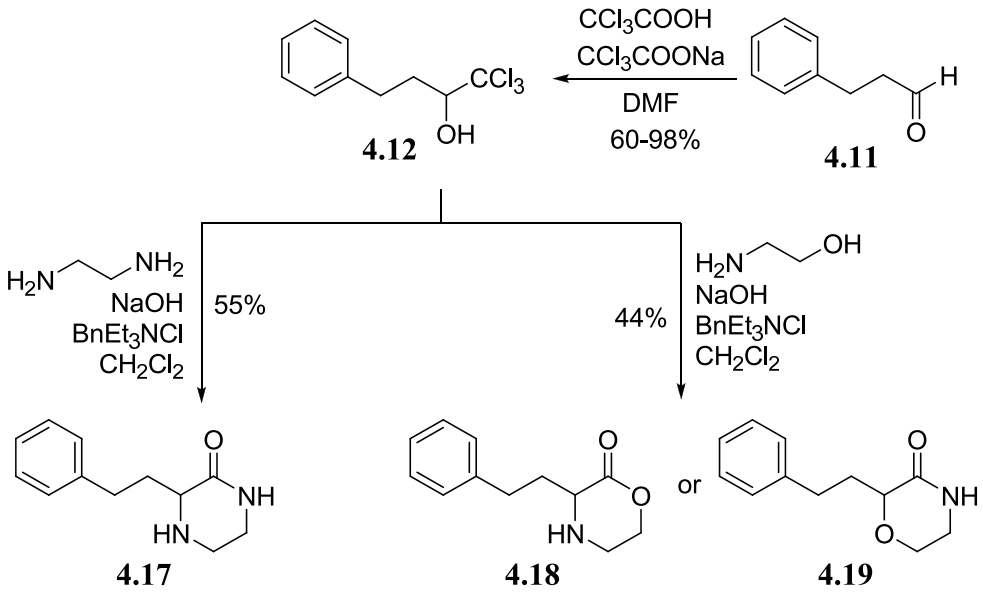


Scheme 81. Stepwise synthesis of α-azido amide 4.14 to confirm its structure.

4.3.3 Lactams via Hybrid Bargellini Reactions

With the modified Corey-Link reaction confirming the trapping of the proposed dichloroepoxide intermediate with two nucleophiles, we could now attempt our hybrid Bargellini reactions on alkyl substrates. We decided to begin with our test substrate, hydrocinnamaldehyde. Our first attempts using 1,1,1-trichloro-4-phenylbutan-2-ol (**4.12**) by modifying Lai's procedure (using a homogeneous reaction mixture without the use of CH_2Cl_2 or a phase transfer catalyst as in our modified Corey-Link reaction) gave a mixture of products which could not be separated. By deferring back to Lai's biphasic procedure using CH_2Cl_2 and a

phase transfer catalyst we successfully synthesised racemic β-hetero-δ-lactams using both ethanolamine and ethylenediamine as the binucleophile (**Scheme 82**).



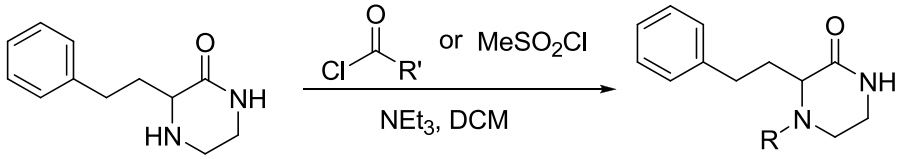
Scheme 82. Lactams *via* a hybrid Bargellini reaction.

We were extremely pleased with the outcome of these reactions, not only because we had synthesised the desired lactams but also because we performed a hybrid-Bargellini reaction on an alkyl substrate, something that was previously thought to be unachievable. We wrongly assumed the structure of the heterocycle of the carbinol with the ethanolamine binucleophile would be the morpholine-2-one (**4.18**), not the lactam (**4.19**), with the more nucleophilic nitrogen attacking the *gem*-dichloroepoxide first, followed by ring formation *via* attack of the oxygen nucleophile (*vide infra*).

4.3.4 N-Alkylation of Racemic β-Hetero-δ-lactams

It has been well documented that piperazin-2-ones are good peptidomimetics[303] and have attracted much attention because of their biological and synthetic applications, as have morpholinones.[304] *N*-Alkylated heterocycles of this type

similarly give significant properties to the molecules, therefore we performed *N*-alkylations to build a library of products which would hopefully prove to have biological activity.



4.17 **4.20-4.24**

R	***(X)***	***Yield (%)***
Ms	**4.20**	31
C(O)Me	**4.21**	88
C(O)Et	**4.22**	82
C(O)^{i}Pr	**4.23**	9
C(O)^{t}Bu	**4.24**	89

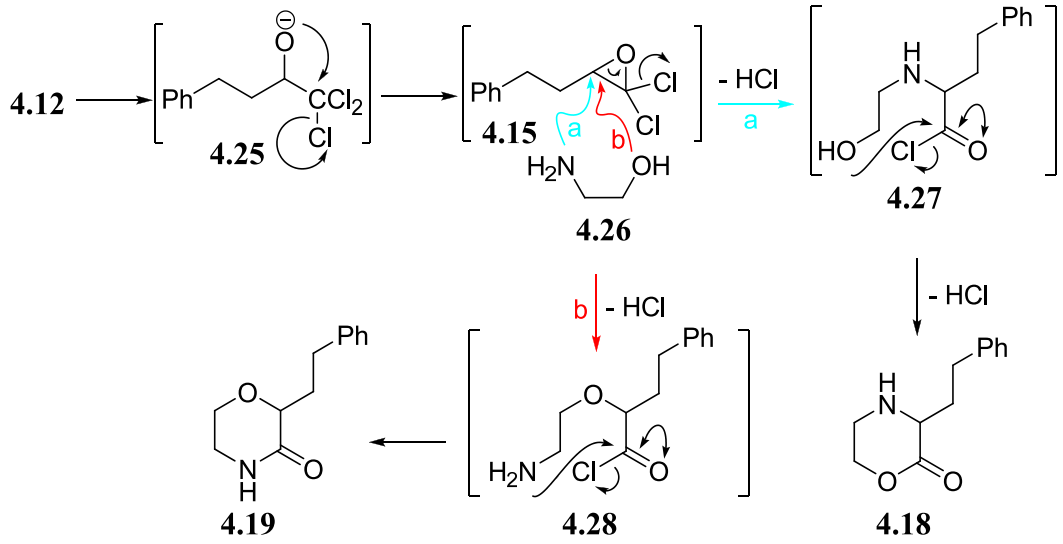
Figure 21. *N*-alkylation of the piperazin-2-one 4.17.

The *N*-acylation of the piperazin-2-one (**4.17**) proved very straightforward and gave high yields for a range of compounds (**Figure 21**). On the other hand, the alkylation of the morpholinone (**4.18/4.19**) was not achieved using any acyl chloride. This was a very surprising result and prompted us to re-evaluate our thought that the ethanolamine would form the lactam preferentially and not the lactam during the hybrid-Bargellini reaction.

4.3.5 Morpholinone (Lactam vs Lactone)

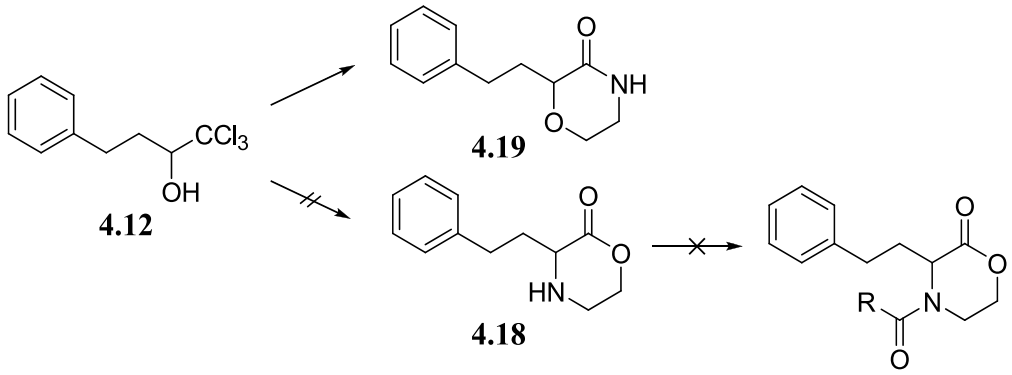
It was important for us to confirm the structure that the hybrid-Bargellini reaction of ethanolamine with our trichlorocarbinol would produce, either the morpholinone (**4.18**) or the lactam (**4.19**). We believe the reaction proceeds through a *gem*-dichloroepoxide intermediate (**4.15**), formed from the basic deprotonation and epoxide formation of the α-trichloromethyl carbinol (**4.12**), which undergoes nucleophilic attack from the binucleophile ethanolamine (**4.26**) in **Scheme 83**. We assumed that as nitrogen is more nucleophilic in character than oxygen, it would ring open the *gem*-dichloroepoxide intermediate *via* the blue

pathway, a (**Scheme 82**), preferentially over ring opening from the less nucleophilic oxygen *via* the red pathway, b (**Scheme 82**).



Scheme 83. Possible pathways during our modified Bargellini reaction with ethanolamine.

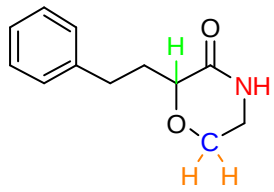
We found a number of reasons, compounded by the fact that the product would not *N*-acylate (**Scheme 84**), which strongly suggested the lactam and the red pathway, pathway b, occurs and not the morpholin-2-one pathway, pathway a (**Scheme 82**).



Scheme 84. Failed *N*-alkylation attempts of 4.12 imply the formation of the lactam (4.19).

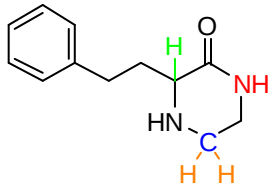
Firstly, the infrared spectrum of the compound in question has an amide peak at 1650 cm^{-1} which strongly suggests we had synthesised the lactam (**4.19**). Indeed, this infrared shift is comparable to that of piperidin-2-one reported by Torra[305], with a carbonyl band at 1660 cm^{-1}. If we had synthesised the morpholin-2-one (**4.18**) then the carbonyl IR band would be in the region of 1730-1750 cm^{-1}, much

like that reported by Nikishin[306] for δ-valerolactone with a carbonyl band at 1730 cm^{-1}. This together with the characteristic ^{1}H & ^{13}C NMR peaks of our ethanolamine derivative in chloroform-*d*:



δ_H: 7.00 (1H, br s, CON*H*), 4.32 (1H, dd, *J* 9.0, 4.0, C*H*OCH$_2$), 3.75 (2H, t, *J* 5.0, OC*H*$_2$CH$_2$NH), δ_C: 61.9 (CHOCH$_2$); and in d_6-DMSO; δ_H: 8.28 (1H, t, *J* 5.5, CON*H*CH$_2$),

compared with the characteristic ^{1}H & ^{13}C NMR peaks of the 3-phenethylpiperazin-2-one (**4.17**) product in chloroform-*d*:



δ_H 6.55 (1H, br s, CON*H*), 3.46-3.36 (2H, m, C*H*CONHC*H*H), 3.13 (1H, dtd, *J* 13.0, 4.0, 0.5, CHNHC*H*H), 2.96 (1H, dddd, *J* 13.0, 9.5, 4.0, 2.0, CHNHCH*H*), 1.90 (1H, br s, CHN*H*), δ_C: 41.4 (CHNHCH$_2$).

highlights a number of interesting points;

1) The stereocentre, highlighted in green, is a distinct dd coupling to only 2 other hydrogens. This suggests the lactam is formed, as there is no splitting by an NH group. If it was a morpholin-2-one then we would expect the stereocentre to be a ddd, as we have seen with all other compounds of this nature (despite the potentially labile nature of amine protons in deuterated solvents), or a multiplet as in our comparison with (**4.17**).

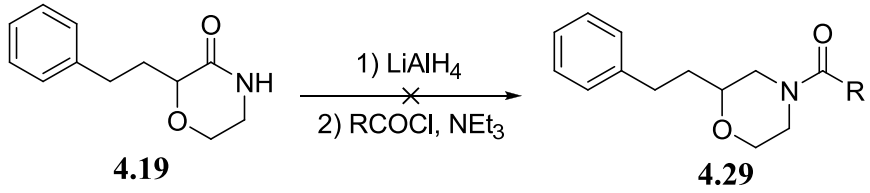
2) The CH_2's within the heterocycle closest to the stereocentre, highlighted in orange, have a distinct triplet. These chemical shifts are further upfield than expected if a morpholinone had been synthesised, as the $COOCH_2$ would be a triplet at a higher chemical shift of around 4 ppm.

3) The carbon spectra show a CH_2 peak at 62 ppm, highlighted in blue, which would correspond to a $CHOCH_2$ and not a $CHNHCH_2$ carbon, like we have seen in our other heterocycles at 42 ppm.

4) There's only one NH, shown in red, and it appears at 7 ppm. This most likely corresponds to a CON*H* and not a CHN*H*CH_2, which would be at around 2 ppm, as we have seen in many of our other heterocycles. However, NH's are known to move about, so this evidence alone is not conclusive.

5) To add to points 3) and 4), when the spectra are recorded in DMSO-d_6, an NH peak at 8.28 ppm and a triplet corresponding to a CONH with an adjacent CH_2 is visible, which would correspond to the lactam. There is also only one stereocentre peak, at 58.3 ppm, in the carbon spectrum.

With this information, the lack of acylation and the IR spectra, we believe there to be enough evidence to assign the compound as the morpholin-3-one. To strengthen our argument a number of manipulations were attempted on the product. If the structure was indeed the lactam (**4.19**), as we now thought, then reduction of the amide to its amine and acylation of the then free amine (to give compounds like **4.29**) should be possible (**Scheme 84**). Unfortunately complications arose during these reactions, we produced a linear compound of unknown structure.



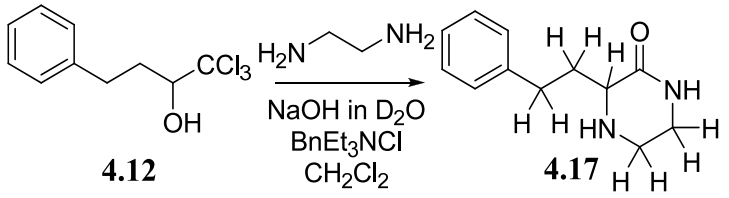
4.19 **4.29**

Scheme 85. Using *N*-alkylations to prove the structure of our ethanolamine derivative.

4.3.6 Racemisation Test

To see whether or not racemisation could occur during these hybrid-Bargellini reactions we subjected the α-trichloromethyl carbinol to the original conditions

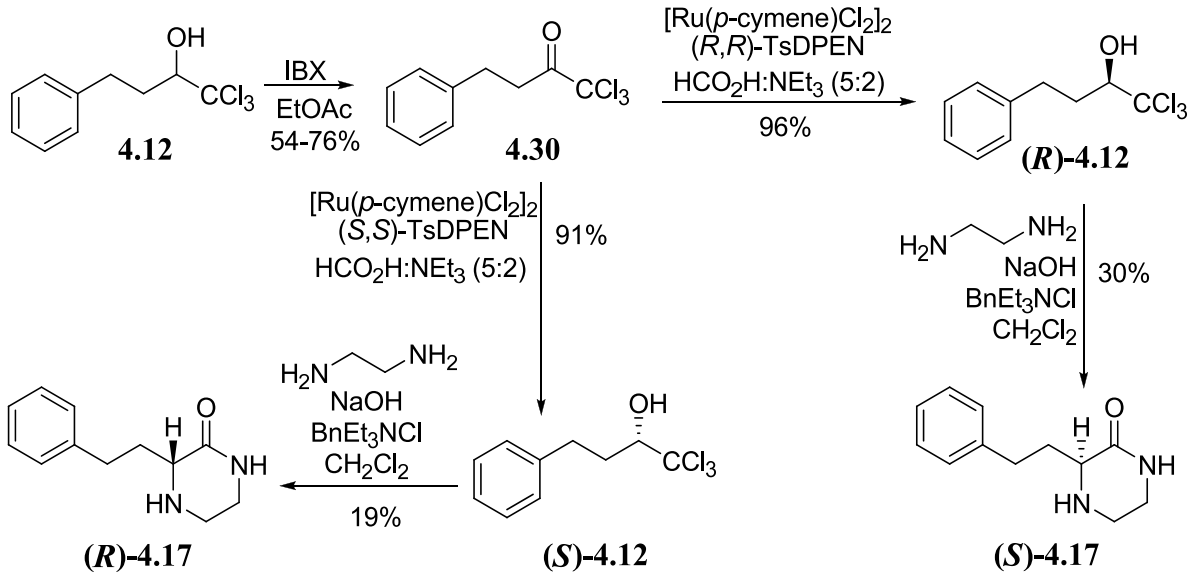
using deuterated water. We used ethylenediamine as our binucleophile and found no incorporation of deuterium during the reaction (**Scheme 86**). Therefore we are confident that no racemisation occurs during these reactions.



Scheme 86. Racemisation test during our hybrid-Bargellini reactions.

4.4 Enantiomerically Enriched Piperazin-2-ones

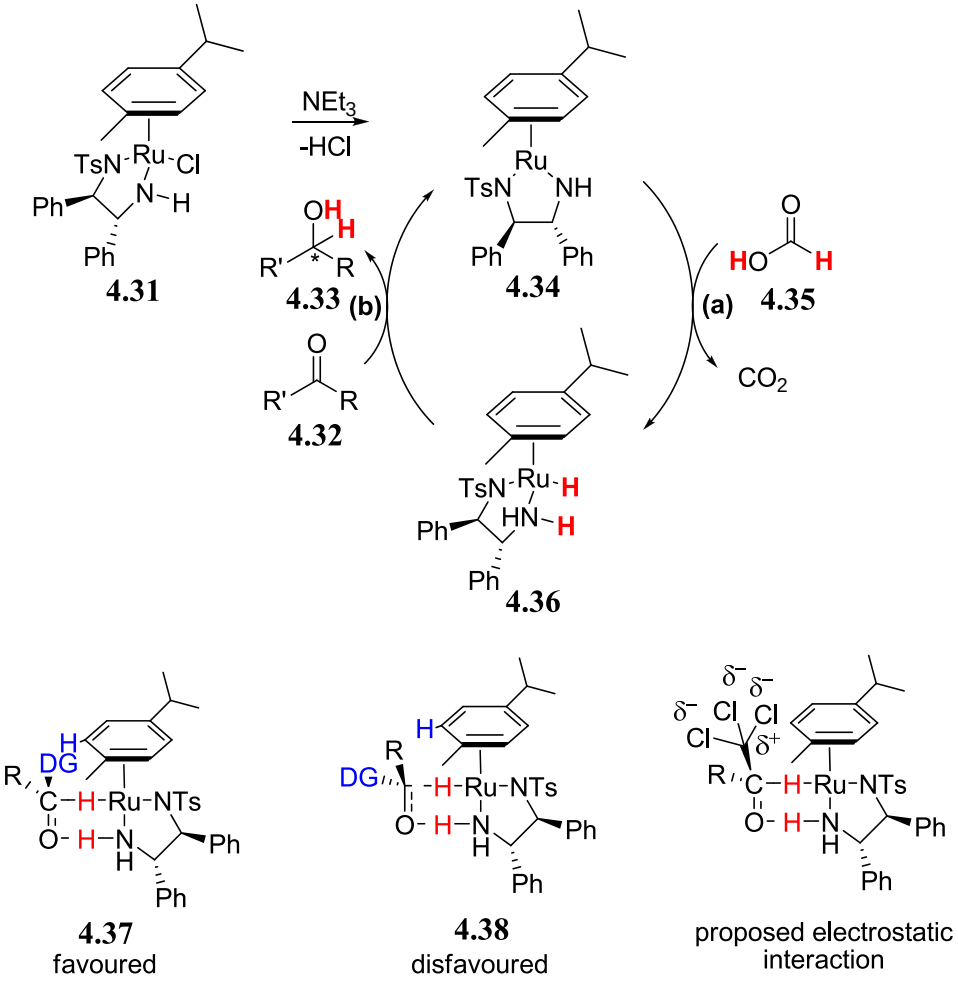
Herein we describe the novel synthesis of enantiomerically enriched piperazin-2-ones using transfer hydrogenation and a hybrid-Bargellini reaction. (*S*)-3-phenylethylpiperazin-2-one (**(*S*)-4.17**) and (*R*)-3-phenethylpiperazin-2-one (**(*R*)-4.17**) were synthesised (**Scheme 86**) from the corresponding trichloroketone (**4.30**), realised by refluxing the racemic α-trichloromethyl carbinol (**4.12**) with IBX in ethyl acetate, followed by asymmetric reduction.



Scheme 87. Asymmetric synthesis of piperzinones using transfer hydrogenation and a hybrid-Bargellini reaction.

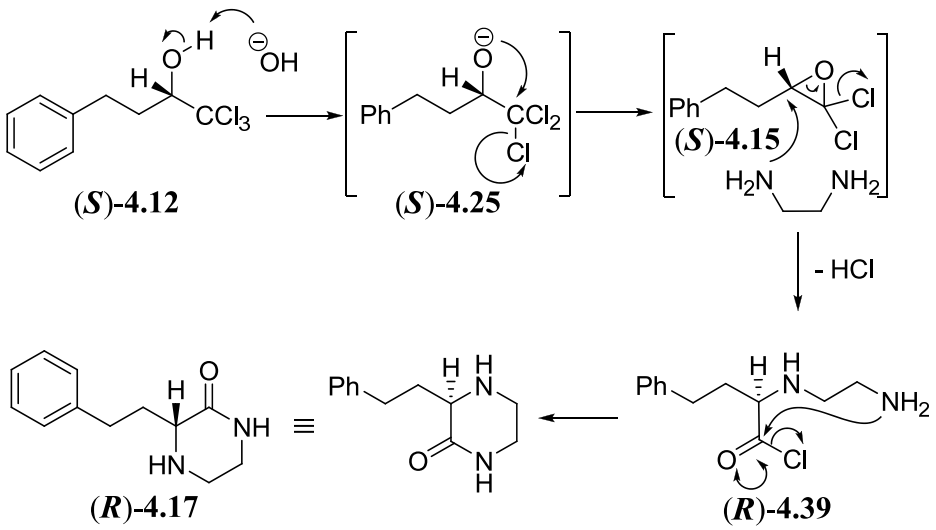
Catalytic asymmetric transfer hydrogenation[307-312] of the ketone with the *in situ* generation of either (*R*,*R*)-TsDPENRu(*p*-cymene)Cl or (*S*,*S*)-TsDPENRu(*p*-

cymene)Cl gives the corresponding enantiomerically enriched (*R*) and (*S*) α-trichloromethyl carbinols, **(*R*)-4.12** and **(*S*)-4.12** respectively. We believe the reaction proceeds *via* the CCl_3 of the carbinol acting as the directing group through a favoured electrostatic interaction with the catalyst (**4.37**) during the hydrogenation cycle (**Scheme 88**).



Scheme 88. Catalytic cycle during the transfer hydrogenation reactions (top) with the proposed electrostatic interaction with trichloroketones (bottom).

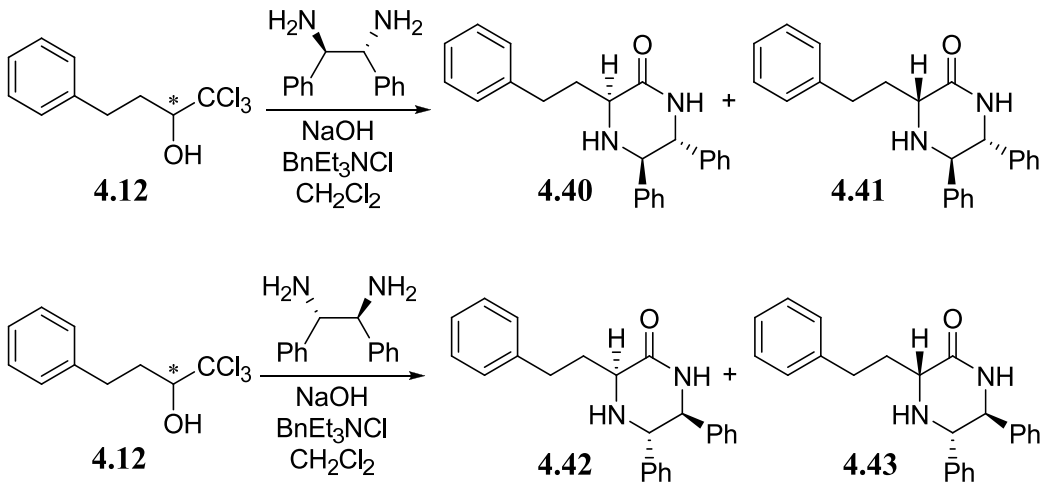
We propose the formation of the heterocycle, and the hybrid-Bargellini reactions, proceeds through a *gem*-dichloroepoxide intermediate with complete inversion of stereochemistry (**Scheme 89**) giving e.e's greater than 95%. All reactions proceed in high yields in only 4 steps from the corresponding aldehyde.



Scheme 89. Proposed hybrid-Bargellini mechanism.

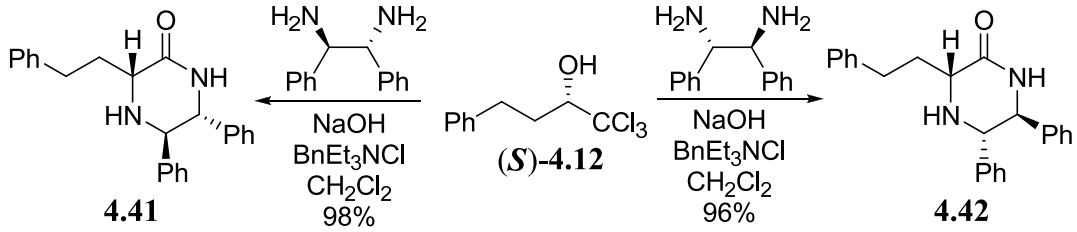
The synthesis of multiple stereocentres within a heterocycle is also of great importance, both synthetically and medicinally.[313-314] With our successful asymmetric synthesis of the α-substituted-β-hetero-δ-lactams we wished to utilise the chemistry to see if we could introduce 2 new stereocentres within the molecule using an enantiopure binucleophile, which would furnish an asymmetric α,γ,δ-substituted-β-hetero-δ-lactam.

We first wanted to check that the reaction of the racemic α-trichloromethyl carbinol would proceed with a chiral binucleophile. With the availability of (1*R*, 2*R*)-1,2-diphenylethane-1,2-diamine ((*R*,*R*)-DPEN) and (1*S*, 2*S*)-1,2-diphenylethane-1,2-diamine ((*S*,*S*)-DPEN) we proceeded with our hybrid-Bargellini reaction using racemic α-trichloromethyl carbinol (**4.12**). Indeed, the reaction of the enantiopure diamine under our conditions proceeded to give a mixture of the two possible diastereoisomers (**Scheme 90**) which were separable by column chromatography.



Scheme 90. Hybrid-Bargellini reaction using enantiopure diamine and racemic alkyl α-trichloromethyl carbinol.

This was extemely encouraging, and so we proceeded to perform the hybrid-Bargellini reaction using a chiral diamine on an enantiopure α-trichloromethyl carbinol. The reaction of a stereochemically pure α-trichloromethyl carbinol ((***S***)-**4.12**) with either (*R*,*R*)-DPEN or (*S*,*S*)-DPEN furnishes the asymmetric α,γ,δ-substituted-β-hetero-δ-lactams **4.41** and **4.42** respectively (**Scheme 91**) in excellent yields.



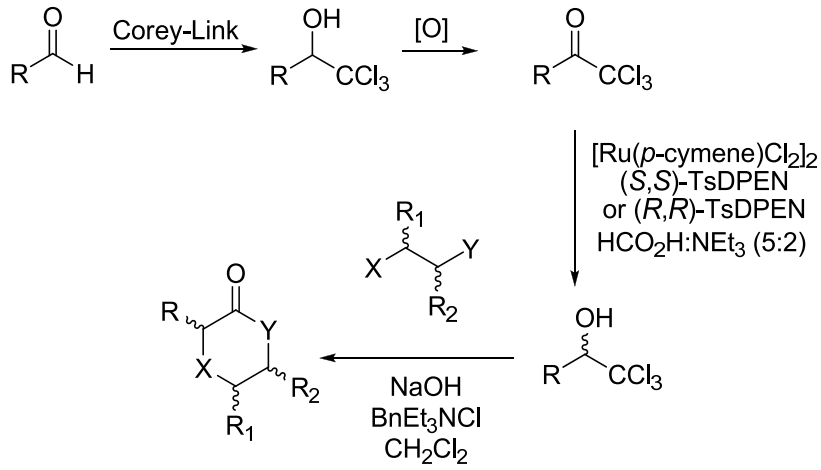
Scheme 91. Synthesis of a three stereocentered lactam using our hybrid-Bargellini reaction with enantio-enriched α-trichloromethyl carbinol and chiral binucleophile (diamine) source.

4.5 Conclusions and Future Work

We have shown that it is possible to synthesise stereochemically pure heterocycles containing up to 3 stereocentres using α-trichloromethyl carbinols and asymmetric transfer hydrogenation chemistry from simple starting materials. Developments of this type of chemistry will undoubtedly lay the foundations to

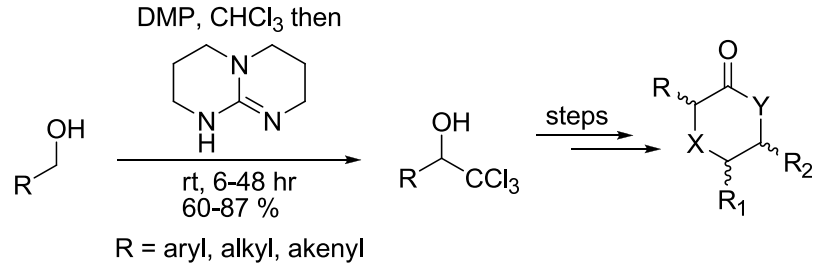
produce further non-racemic substituted heterocycles which will be important both synthetically and biologically.

Future work should include an investigation into the scope of the reaction using a range of α-trichloromethyl carbinols and binucleophiles, which will undoubtedly enhance the applicability of this chemistry. We envisage the synthesis of a wide range of asymmetric heterocycles using this type of chemistry (**Scheme 92**).



Scheme 92. Future work: expanding the scope of the reaction.

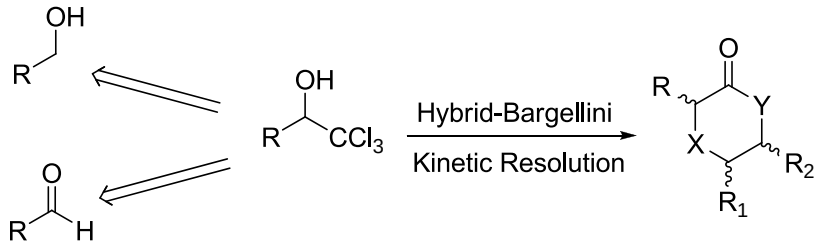
Also, with the recent publication by Snowden of a convenient one-pot synthesis of trichloromethyl carbinols from primary alcohols with complete stereochemical fidelity (**Scheme 93**),[315] the range of heterocycles available from our method, using simple starting materials, is potentially vast.



Scheme 93. Future work: starting from primary alcohols.

Also of interest is the kinetic resolution of the racemic carbinol using chiral, stereochemically pure nucleophiles. This could afford substituted heterocycles

successively eliminating the need for an oxidation and hydrogenation step (**Scheme 94**), a very exciting thought.



Scheme 94. Potential for kinetic resolution of heterocycles.

4.6 References

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Chapter 5 – Experimental

5.1 General Experimental

All the reagents used were purchased from the Sigma-Aldrich, Alfa-Aesar or Fluorochem Chemical Company and unless stated otherwise were used as received.

^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance DPX-400 Fourier transform spectrometer using an internal clock with a QNP probe, X-Win NMR software package, and Icon NMR interface, unless stated otherwise. Chemical shifts are quoted in parts per million (ppm) downfield from tetramethylsilane. Solvents were used as an internal standard when assigning NMR spectra (δ_H: $CDCl_3$ 7.26 ppm, CD_3OD 3.31 ppm, d^6-DMSO 2.50 ppm, D_2O 4.79 ppm; δ_C: $CDCl_3$ 77.1 ppm, CD_3OD 49.0 ppm, d^6-DMSO 39.5 ppm). Coupling constants (*J*) are quoted in Hertz (Hz), rounded to the nearest 0.5 Hz, and characterised with either Bruker biospin Topspin Version 2.1 or MestRe-C V 4.5.6. Abbreviations used in the descriptions of spectra are as follows; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, *i* = ipso, *o* = ortho, *m* = meta, *p* = para, *ax.* = axial and *eq.* = equatorial. ^{13}C-NMR spectra were recorded with broadband proton decoupling and spectra were assigned on the basis of COSY, PENDANT and HMQC spectra.

Infrared spectra were recorded on a Nicolet Avatar 320 FT-IR spectrophotometer using EZ OMNIC software package 1, and are quoted in wavenumber (cm^{-1}). Optical rotations were recorded on an Optical Activity Ltd. AA-1000 millidegree auto-ranging polarimeter (using the sodium D line; 589 nm) and $[\alpha]_D$s are given in units of 10^{-1} deg cm^2 g^{-1}. The samples were made using spectroscopic grade MeOH or chloroform.

Mass spectra were obtained *via* ESI on a Bruker Esquire 2000 with Hyphenation Star Version 3.0 Interface and Bruker Daltonics Esquire Version 5.2 software. Accurate mass spectra were obtained using a Bruker micro-TOF ESI attached to a time of flight (TOF) analyser.

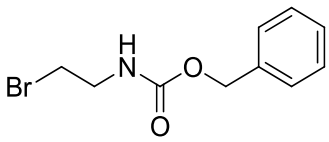
Melting points for solid crystalline products were determined on a Stuart Scientific SMP10 Digital Melting Point Apparatus, with 3 runs of each compound, and a range given in ^{o}C rounded to the nearest degree. CHN elemental analyses were carried out by Warwick Analytical Services.

Thin Layer Chromatography (TLC) was performed using silica (0.25 mm) coated alumina plates.

5.2 Chapter 2 Experimental

5.2.1 Thialactam derivatives

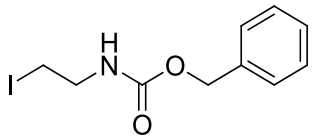
N-Benzyloxycarbonyl-2-bromoethylamine (**2.70**)



Sodium bicarbonate (4.2 g, 50.0 mmol) was added portion wise to a stirred mixture of 2-bromoethylamine hydrobromide (10.0 g, 48.8 mmol) in H_2O (100 mL) and the mixture was cooled in an ice bath. Benzylchloroformate (9 mL, 63.9 mmol) was added dropwise to the mixture followed by 1 M NaOH (50 mL) with vigorous stirring over a period of 2 h. The precipitate formed was collected and dissolved in EtOAc (50 mL), dried over sodium sulfate, filtered, concentrated *in vacuo* and recrystallised from Petroleum ether 40-60 to give a white crystalline solid (12.5 g, 48.4 mmol, 99%); m.p.: 46-47 ^{o}C; υ_{max} (cm^{-1}): 3305 (NH), 1680 (CO), 1537 (COO), 1263 (CH_2) 746, 709 (Ph); δ_H (400 MHz, $CDCl_3$) 7.32-7.38

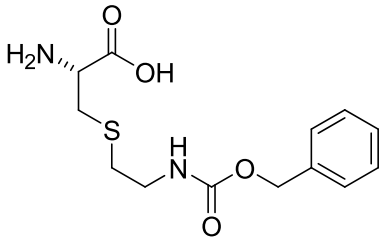
(5H, m, Ph), 5.28-5.13 (1H, br, N*H*), 5.12 (2H, s, CH_2Ph), 3.61 (2H, q, *J* 6.0, CH_2NH) and 3.47 (2H, t, *J* 6.0, BrCH_2); δ_C (100 MHz, $CDCl_3$) 156.8 (*C*O), 136.2 (*i*-Ph), 128.6 (Ph), 128.2 (Ph), 128.0 (Ph), 67.8 (*C*H_2Ph), 42.8 (*C*H_2NH) and 31.4 (Br*C*H_2); *m/z* 258.1 ($M + H^+$) & 280.1 ($M + Na^+$). This data is consistent with that previously reported.[164]

N-Benzyloxycarbonyl-2-iodoethylamine (**2.71**)



N-Benzyloxycarbonyl-2-bromoethylamine (2.3 g, 8.9 mmol) was refluxed for 1.5 h in acetone (30 mL) with potassium iodide (1.5 g, 8.9). After cooling the solution was diluted with diethyl ether and quickly filtered to remove potassium bromide. The mother liquor was washed with H_2O and concentrated *in vacuo* and used without further purification.

2-Amino-3-(2-benzyloxycarbonylamino-ethylsulfanyl)-propionic acid (**2.73**)

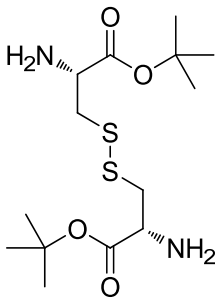


To a stirred solution *L*-cysteine hydrochloride (0.1 g, 0.7 mmol) in H_2O (5 mL) was added **2.71** (0.2 g, 0.7 mmol) in ethanol (10 mL). The *p*H of the solution was adjusted to 10 by dropwise addition of 5 M NaOH and the mixture left stirring for 2 h. The solution was acidified to *p*H 4 using 1 M HCl and the precipitated product was filtered and dried *in vacuo* to give a white crystalline solid (0.2 g,

0.5 mmol, 82%); υ_{max} (cm^{-1}): 3335 (CONH), 3030 (NCH_2), 1688 (C=O), 1594, 1546 (Ph), 1269 (OH), 1143 (CO), 736 (Ph); δ_H (400 MHz, D_2O/NaOH) Unsuitable for characterisation, peaks at 7.42, 5.11, 3.36, 3.34, 2.81, 2.77, 2.67; δ_C (100 MHz, D_2O/NaOH) Unsuitable for characterisation.

General Method A: Synthesis of Cbz-L-Cys-O^{t}Bu

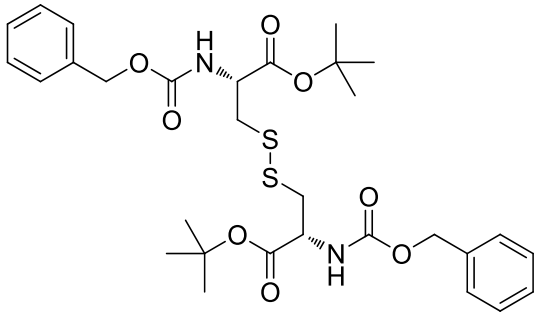
L-Cystine-O^{t}Bu (**2.88**)



tert-Butyl acetate (100 mL) was added to a stirred solution of L-cystine (10.0 g, 41.6 mmol) in 70% v/v perchloric acid (16.6 mL) at ambient temperature behind a blast shield. After 30 min, the solution became clear, and after 3 h a white solid appeared. Stirring was continued for another 18 h and the reaction mixture was cooled on ice for 15 minutes. H_2O (100 mL) was added followed by EtOAc (100 mL) until the entire solid was dissolved, and the *p*H was adjusted from 1 to 9 using 10 M NaOH. The organic layer was separated and the aqueous layer was extracted further with EtOAc (2 x 70 mL). The organic layers were combined and dried over sodium sulfate, filtered and concentrated *in vacuo* to give a light yellow oil (14.6 g, 41.4 mmol, 99%); $[\alpha]_D^{15}$ (c = 1, MeOH) − 7.1; υ_{max} (cm^{-1}): 2975 ($COC(CH_3)_3$), 1719 (OCOC), 1394, 1396 ($C(CH_3)_3$); δ_H (400 MHz, $CDCl_3$) 3.66 (2H, dd, *J* 8.0, 4.5, 2 × C*H*NH_2), 3.12 (2H, dd, *J* 13.5, 4.5, 2 × C*H*$_2$S-), 2.86 (2H, dd, *J* 13.5, 8.0, 2 × C*H*$_2$S-), 1.72 (4H, br s, 2 × N*H*$_2$) and 1.47 (18H, s, 2 × $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 172.9 (*C*O) 81.8 ($OC(CH_3)_3$), 54.3 (*C*HNH_2), 44.05 (CH_2S) and 28.04 ($C(CH_3)_3$); *m/z* ($C_{14}H_{29}N_2O_4S_2$ (M + H^+) requires

353.1563) found 353.1563, ($C_{14}H_{28}N_2NaO_4S_2$ (M + Na^+) requires 353.1383) found 353.1382. This data is consistent with that previously reported.[173]

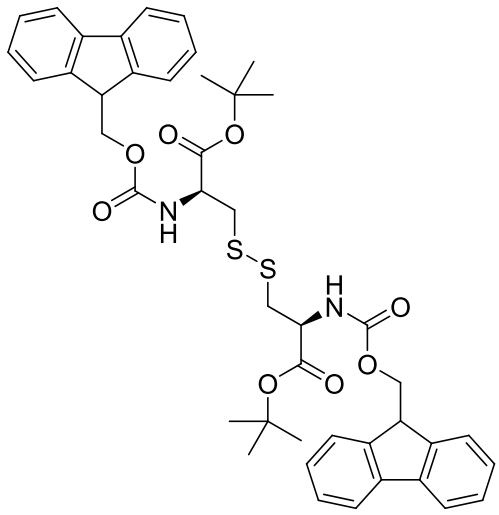
Cbz-L-Cystine-O^{t}Bu (**2.89**)



To **2.88** (14.7 g, 41.6 mmol) partitioned between sat. aq. $NaHCO_3$ (125 mL) and chloroform (125 mL) at 0 ^oC was added benzylchloroformate (17.5 mL, 124.8 mmol) and allowed to stir for 2 h at room temperature. After this time the aqueous layer was separated and discarded. Pyridine (4.1 mL) was added dropwise to the remaining chloroform layer at 0 ^oC causing effervescence. After complete addition of the pyridine with no more effervescence the solution was successively washed with 1 M H_2SO_4, distilled H_2O and diluted aq. $NaHCO_3$. After drying over sodium sulfate, and concentrating *in vacuo* the residue was purified by silica column chromatography (eluent; EtOAc to EtOAc:MeOH (9:1)) to give an off white crystalline solid (23.5 g, 37.8 mmol, 91%); m.p. 73-74 ^oC; $[\alpha]_D^{16}$ (c = 1, MeOH) -58.5; $[\alpha]_D^{24}$ (c = 1, MeOH) -66.8; υ_{max} (cm^{-1}): 3369 (NH), 2977 ($COC(CH_3)_3$), 1707 (OCON, CO), 1516 (CH), 1153 (CO); δ_H (400 MHz, $CDCl_3$) 7.38-7.27 (10H, m, 2 × Ph), 5.68 (2H, br d, *J* 7.5, 2 × N*H*CH) 5.10 (4H, s, 2 × CH_2OCO), 4.56-4.50 (2H, m, 2 × NHC*H*), 3.18-3.09 (4H, m, 2 × CH_2S) and 1.46 (18H, s, 2 × C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 169.3 (CH*C*OOC$(CH_3)_3$), 155.7 (O*C*ONHCH), 135.2 (*i*-Ph), 128.4 (Ph), 127.5 (Ph), 126.9 (Ph), 82.9 (O*C*$(CH_3)_3$), 67.0 (*C*H_2OCO), 54.2 (CONH*C*HCO), 41.5 (*C*H_2SS), 27.9 (C(*C*H_3)$_3$); *m/z* ($C_{30}H_{40}N_2NaO_8S_2$ (M + Na^+) requires 643.2118)

found 643.2134. This compound is known but has previously only been reported with m.p and ^{1}H NMR data (90 MHz), which is consistent with that reported here.[172]

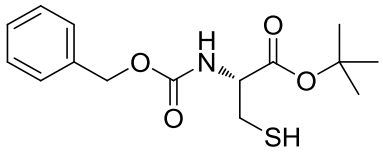
Fmoc-L-Cystine-O^{t}Bu (**2.90**)



2.88 (7.0 g, 20 mmol) and fluorenylmethoxycarbonyl chloride (10.2 g, 40 mmol) were dissolved in THF (50 mL) under nitrogen. The reaction was cooled in an ice bath and NMM (4.5 mL, 40 mmol) was slowly added to the solution. The resulting mixture was stirred for 16 h. Ethyl acetate (200 mL) was added to the mixture, which was then washed with 5% aq. potassium hydrogen sulfate (4 x 50 mL) and water (3 x 50 mL). The organic layer was separated, dried over sodium sulfate, and concentrating *in vacuo* yielding a crude yellow liquid which was purified by silica column chromatography (eluent; EtOAc to EtOAc:MeOH (9:1)) to give an off white solid (14.2 g, 18 mmol, 90%); m.p. 150-151 ºC; $[\alpha]_D^{16}$ (c = 1, MeOH) -30.2; υ_{max} (cm^{-1}): 3335 (NH), 2977 (COC(CH$_3$)$_3$), 1720 (OCON, CO), 1516 (CH), 1151 (CO); δ_H (400 MHz, CDCl$_3$) 7.76 (4H, d, *J* 7.5, 2 × C*H*(C)(C)C*H*), 7.62 (4H, d, *J* 7.5, 2 × C*H*(C)CH(C)C*H*), 7.41 (4H, t, *J* 7.0, 2 × C*H*CH(C)(C)CHC*H*), 7.33 (4H, t, *J* 7.5, 2 × C*H*CH(C)CH(C)CHC*H*), 5.71 (2H, d, *J* 7.0, 2 × N*H*CH), 4.57 (2H, dd, *J* 13.0, 5.5, 2 × C*H*NH), 4.41-4.33 (4H, m, 2

× OCH_2), 4.23 (2H, t, *J* 7.0, 2 × OCH_2CH), 3.28-3.19 (4H, m, 2 × CH_2S) and 1.51 (18H, s, 2 × $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 169.1 ($CHCOOC(CH_3)_3$), 155.7 (O*C*ONHCH), 143.7 ((*C*)CH(*C*)), 141.4 ((*C*)(*C*)), 127.4 (Ph), 127.0 (Ph), 126.2 (Ph), 119.9 (*C*H(C)CH(C)*C*H), 82.9 ($OC(CH_3)_3$), 67.0 (CH_2OCO), 54.2 (CONH*C*HCO), 41.7 (CH_2SS), 27.9 ($C(CH_3)_3$); *m/z* ($C_{44}H_{48}N_2NaO_8S_2$ ($M + Na^+$) requires 819.2746) found 819.2746. This data is consistent with that previously reported.[168]

Cbz-L-Cys-O^{t}Bu (**2.91**)



Reduction of L-Cystine, Method I – Triphenylphosphine, mercaptoethanol

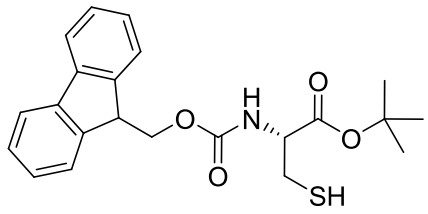
To a stirred solution of **2.89** (6.2 g, 10.0 mmol) in 100 mL of THF was added Ph_3P (2.6 g, 10.0 mmol), 2-mercaptoethanol (1.24 mL, 10.0 mmol), and water (100 mL), and the reaction mixture was stirred at 50 °C under nitrogen for 16 h before being concentrated *in vacuo*. The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:9) to EtOAc) to give a colourless oil (4.4 g, 7.1 mmol, 71%).

Reduction of L-Cystine, Method II – PBu_3 Method

To a stirred solution of **2.89** (11.7 g, 18.8 mmol) in THF (100 mL) under nitrogen was added PBu_3 (7 mL, 28.1 mmol). After 60 minutes H_2O (10 mL) was added and the mixture stirred at room temperature until the reaction was complete (17 h). The THF was removed *in vacuo* and the residue diluted with EtOAc (100 mL). The resulting mixture was washed successively with 10% citric acid, H_2O and brine. The organic extracts were combined and dried over

sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:9) to EtOAc) to give a colourless oil (11.7 g, 18.8 mmol, > 99%); $[\alpha]_D^{24}$ (c = 1, MeOH) -23.1; υ_{max} (cm^{-1}): 3342 (NH), 2978 ($COC(CH_3)_3$), 2573 (SH), 1712 (OCON, CO), 1499 (CH), 1150 (CO); δ_H (400 MHz, $CDCl_3$) 7.31-7.40 (5H, m, Ph), 5.96 (1H, d, *J* 7.5, N-*H*CH), 5.15 (2H, s, C*H*$_2$Ph), 4.59 (1H, dt, *J* 7.5, 4.0, C*H*NH), 2.97 (2H, dd, *J* 9.0, 4.0, CHC*H*$_2$SH), 1.51 (s, 9H, C(C*H*$_3$)$_3$) and 1.37-1.41 (1H, m, S*H*); δ_C (100 MHz, $CDCl_3$) 168.9 (CH*C*OOC$(CH_3)_3$), 155.7 (O*C*ONHCH), 136.2 (*i*-Ph), 128.5 (Ph), 128.2 (Ph), 128.1 (Ph), 82.9 (O*C*$(CH_3)_3$), 67.0 (*C*H_2OCO), 55.5 (CONH*C*HCO), 28.0 (C(*C*H_3)$_3$) and 27.44 (*C*H_2SH); *m/z* ($C_{15}H_{21}NNaO_4S$ (M + Na^+) requires 334.1083) found 334.1086; 278.1. This compound is known but has previously been reported without any characterisation.[316]

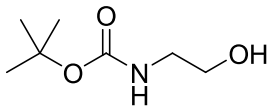
Fmoc-L-Cys-O^{t}Bu (**2.92**)



Fmoc-L-Cys-O^{t}Bu (**2.92**) was synthesised according to cystine reduction method I or method II using **2.90** (8.0 g, 10 mmol). In each case the residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:9) to EtOAc) to give a colourless oil (method I: 4.2 g, 5.3 mmol, 53%; method II: 0.7 g, 0.9 mmol, 9%); $[\alpha]_D^{24}$ (c = 1, MeOH) -30.4; υ_{max} (cm^{-1}): 3342 (NH), 2978 ($COC(CH_3)_3$), 2570 (SH), 1722 (OCON, CO), 1501 (CH), 1150 (CO); δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* 7.5, C*H*(C)(C)C*H*), 7.62 (2H, d, *J* 7.5, C*H*(C)CH(C)C*H*), 7.41 (2H, t, *J* 7.0, C*H*CH(C)(C)CHC*H*), 7.33 (2H, t, *J* 7.5, C*H*CH(C)CH(C)CHC*H*), 5.71 (1H, d, *J* 7.0, N*H*CH), 4.57 (1H, dd, *J* 13.0, 5.5, C*H*NH), 4.41-4.33 (2H, m, OC*H*$_2$), 4.23 (1H, t, *J* 7.0, OCH$_2$C*H*), 3.08-2.89 (2H, m, 2 × C*H*$_2$S), 1.51 (9H, s,

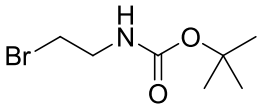
$CO_2C(CH_3)_3$) and 1.38 (1H, t, *J* 9.0, SH); δ_C (100 MHz, $CDCl_3$) 169.0 (CH*C*OOC$(CH_3)_3$), 155.7 (O*C*ONHCH), 143.8 ((*C*)CH(*C*)), 141.3 ((*C*)(*C*)), 127.6 (Ph), 127.0 (Ph), 125.8 (Ph), 119.9 (*C*H(C)CH(C)*C*H), 82.9 (O*C*$(CH_3)_3$), 67.0 (*C*H_2OCO), 55.2 (CONH*C*HCO), 47.1 (*C*HCH$_2$O), 27.9 (C(*C*$H_3)_3$) and 27.4 (CH_2SH); *m/z* ($C_{22}H_{25}NNaO_4S$ (M + Na^+) requires 422.1396) found 422.1398. This data is consistent with that previously reported.[316]

N-(*tert*-Butoxycarbonylamino)ethanol (**2.94**)



To a solution of ethanolamine (3 mL, 50 mmol) in a 1:1 mixture of THF/H_2O (100 mL), triethylamine (8.4 mL, 60 mmol) and Boc_2O (13 g, 60 mmol) were added consecutively at 0 °C. After 30 min, the solution was stirred overnight at room temperature. The turbid solution was extracted with Et_2O (2 × 100 mL), the aqueous layer was acidified to ~*p*H 4 by careful addition of half sat. citric acid at 0 °C and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:1) to EtOAc) to give a colourless oil (4.4 g, 27 mmol, 54%); υ_{max} (cm^{-1}): 3331 (NH), 3253 (OH), 2978 (COC$(CH_3)_3$), 1714 (OCON, CO), 1499 (CH), 1153 (CO); δ_H (400 MHz, $CDCl_3$) 4.92 (1H, s, N*H*), 3.78-3.65 (2H, s, C*H*$_2$OH), 3.39-3.23 (2H, m, NHC*H*$_2$), 2.33 (1H, s, OH) and 1.45 ((9H, s, C(C*H*$_3)_3$); δ_C (100 MHz, $CDCl_3$) 156.6 (NH*C*OOC$(CH_3)_3$), 79.6 (NHCOO*C*$(CH_3)_3$), 62.3 (*C*H_2OH), 43.3 (NH*C*H$_2$), 28.3 (C(*C*$H_3)_3$); *m/z* ($C_7H_{15}NO_3$ (M + H^+) requires 162.1124) found 162.1126. This data is consistent with that previously reported.[317]

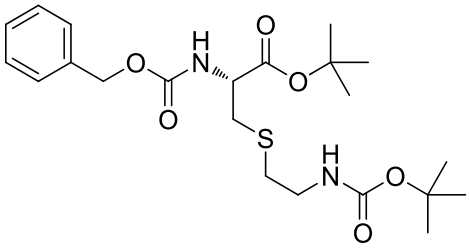
N-(*tert*-Butoxycarbonyl)-2-bromoethylamine (**2.95**)



A solution of di-*tert*-butyl dicarbonate (20.5 g, 94 mmol) in MeOH (60 ml) was added over a period of 30 minutes to a stirred solution of 2-bromoethylamine hydrobromide (12.3 g, 60.0 mmol) and NEt_3 (13.91 ml, 100 mmol) in MeOH (60 mL). After stirring at room temperature for 18 h, the reaction mixture was concentrated *in vacuo*. H_2O (100 mL) was added to the residue and extracted with dichloromethane (3 × 30 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:9) to EtOAc) to give a colourless oil (12.1 g, 54.4 mmol, 90%); υ_{max} (cm^{-1}): 3331 (NH), 2978 ($COC(CH_3)_3$), 1712 (OCON, CO), 1499 (CH), 1150 (CO); δ_H (400 MHz, $CDCl_3$) 5.34-5.14 (1H, br s, N*H*), 3.49-3.34 (2H, m, CH_2NH), 3.34-3.23 (2H, m, BrCH_2) and 1.33 (9H, s, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 155.6 (NH*C*OOC$(CH_3)_3$), 79.5 (NHCOO*C*$(CH_3)_3$), 42.3 (*C*H_2NHCO), 32.3 (Br*C*H_2CH_2), 28.3 (C(*C*$H_3)_3$); *m/z* ($C_7H_{14}{}^{79}BrNNaO_2$ ($M + Na^+$) requires 246.0100) found 246.0102. This data is consistent with that previously reported.[317]

General Method B: Thiol **2.91** coupling with suitable alkyl halide

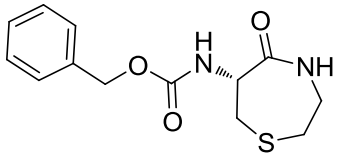
5-[(*tert*-Butyloxycarbonyl)amino]-ethane-2-Benzyloxycarbonylamino-3-mercapto-propionic acid *tert*-butyl ester (**2.96**)



2.91 (3.8 g, 12.3 mmol) and **2.95** (2.8 g, 12.3 mmol) were combined and stirred in EtOAc (55 mL) under nitrogen. A solution of tetra-N-butylammonium bromide (15.8 g, 49.1 mmol) in $NaHCO_3$ (0.5 M, 55 mL) was added after stirring for 10 minutes, keeping the *p*H to 8.5. The mixture was stirred under nitrogen at room temperature for 16 h. The organic layer was separated, washed with H_2O (3 × 30 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:9) to EtOAc) to give a colourless oil (3.8 g, 8.4 mmol, 68%); $[\alpha]_D^{26}$ (c = 1, MeOH) -22.9; υ_{max} (cm^{-1}): 3331 (NH), 2977, 2931 ($COC(CH_3)_3$), 1697 (OCON, CO), 1508 (CH), 1392, 1366, 1343 ($C(CH_3)_3$), 1152 (CO); δ_H (400 MHz, $CDCl_3$) 7.40-7.27 (5H, m, Ph), 5.77 (1H, d, *J* 6.0, CH_2OCONH), 5.13 (2H, s, CH_2Ph), 5.01-5.11 (1H, br s, CH_2NH) 4.48 (1H, dt, *J* 12.5, 5.5, CHNH), 3.38-3.16 (2H, m, CH_2NH), 3.01 (1H, dd, *J* 14.0, 4.5, CHCHHS), 2.95 (1H, dd, *J* 13.5, 5.5, CHCHHS) 2.66 (2H, t, *J* 5.5, SCH_2CH_2NH), 1.49 (s, 9H, $C(CH_3)_3$) and 1.45 (s, 9H, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 169.5 ($CHCOO^tBu$), 155.8 (NHCO) 136.3 (*i*-Ph), 128.5 (Ph), 128.18 (*p*-Ph), 128.15 (Ph), 82.8 ($CHCOOC(CH_3)_3$), 79.3 ($NHCOOC(CH_3)_3$, 66.9 (CH_2OCO), 54.4 (CONHCHCO), 39.6 (CH_2NHCO), 34.5 ($CHCH_2S$), 33.1 (SCH_2CH_2NH) 28.4 and 27.9 (2 × CH_3); *m/z* ($C_{22}H_{34}N_2NaO_6S$ ($M + Na^+$) requires 477.2030) found 477.2037. This compound has not previously been reported.

General Method C: Deprotection of Boc and ^{t}Bu groups and ring closure

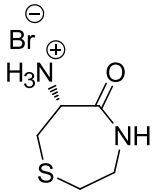
(*R*)-6-(Carboxybenzylamino)-[1,4]-thiazepan-5-one (**2.97**)



To a solution of **2.97** (1.6 g, 3.6 mmol) in anisole (9.8 mL, 90.0 mmol) was added trifluoroacetic acid (14.7 mL, 197.9 mmol) in three portions and allowed to stand for 2 h and concentrated *in vacuo*. Diethyl ether (3 × 25 mL) was added and the solvent removed by decantation to give a viscous white residue. DMF (15 mL) was added and the mixture was stirred for 1 h at 0 ºC. Diphenyl phosphorazidate (1.2 mL, 5.4 mmol) was added followed by *N*-methylmorpholine (1.6 mL, 14.5 mmol) and stirred overnight. To this solution was added EtOAc (25 mL) and H_2O (25 mL). The organic layer was collected, washed with brine and aqueous sodium bicarbonate (25 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:1) to EtOAc) to give a viscous liquid (0.7 g, 2.4 mmol, 66%); $[\alpha]_D^{26}$ (c = 1, MeOH) -15.8; υ_{max} (cm^{-1}): 3220 (CONH), 3093, 2948 (CH_2), 1716 (OCON), 1660 (CONH, lactam ring) 1522 (CH_2), 1241, 1225 (CO), 689 (SCH_2); δ_H (400 MHz, $CDCl_3$) 7.35-7.29 (5H, m, Ph), 7.17-7.00 (1H, br s, CHCON*H*CH_2), 6.31 (1H, d, *J* 5.0, N*H*CH), 5.11 (1H, d, *J* 12.5, C*H*HOCO), 5.08 (1H, d, *J* 12.5, CH*H*OCO), 4.75 (1H, ddd, *J* 9.0, 6.0, 2.5, C*H*CONH) 3.68-3.55 (2H, m, NHCH_2CH_2S), 2.85-2.70 (2H, m, CHCH_2S) and 2.68-49 (2H, m, $NHCH_2CH_2$S); δ_C (100 MHz, $CDCl_3$) 174.7 (CH*C*O$NHCH_2$), 155.3 (O*C*ONH), 136.3 (*i*-Ph), 128.6 (Ph), 128.2 (Ph), 128.1 (*p*-Ph), 66.9 (*C*H_2OCO), 57.1 (*C*HCONH), 45.6 (NH*C*H_2), 31.4 (CH*C*H_2S) and 30.5 ($NHCH_2CH_2$S); *m/z* ($C_{13}H_{16}N_2NaO_3S$ ($M + Na^+$) requires 303.0774) found 303.0772. This compound is known but has previously been reported without any characterisation.[318]

General Method D: Cbz deprotection

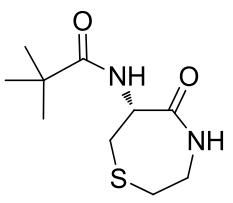
(*R*)-6-(Ammoniumbromide)-[1,4]-thiazepan-5-one (**2.103**)



2.97 (0.7 g, 2.4 mmol) was dissolved in the minimum amount of acetic acid (~1 mL). Hydrogen bromide (40% w/v in acetic acid, 4 mL) was added to this mixture and allowed to stand for 2 h. The solution was washed with diethyl ether and decanted to leave a light yellow precipitate which required no further purification (0.52 g, 2.3 mmol, 95%); m.p.: > 250 ^{o}C; υ_{max} (cm^{-1}): 3194 (CONH), 3003, 2915, 2688, 1967 (CH_2 & $Br^{-}NH_3^{+}$), 1652 (CONH lactam), 1596, 1554, 1471 (NH_3^{+}), 738 (CH_2S); δ_H (400 MHz, D_2O) 4.66 (1H, dd, *J* 10.0, 2.5, N*H*CH), 3.71 (1H, ddd, *J* 16.0, 4.5, 3.0, NHC*H*H), 3.60 (1H, ddd, *J* 16.0, 9.0, 3.0, NHCH*H*), 3.03 (1H, dd, *J* 14.5, 10.0, CHC*H*HS) 2.82 (1H, ddd, *J* 14.5, 2.0, 0.5, CHCH*H*S) and 2.79-2.68 (2H, m, SC*H*$_2$CH$_2$NH); δ_C (100 MHz, D_2O) 55.6 (NH_3^{+}*C*HCO), 44.3 (CONH*C*H$_2$), 29.4 (CHCH$_2$S*C*H$_2$) and 27.1 (NH_3^{+}CH*C*H$_2$SCH$_2$); *m/z* ($C_5H_{11}N_2OS$ [(M – Br)$^{+}$] requires 147.0587) found 147.0590, (C_5H_8NOS [(M – NH_3Br)$^{+}$] requires 130.0321) found 130.0324. This compound has not previously been reported.

General Method E: Acylation reaction of lactam salt with acid chloride

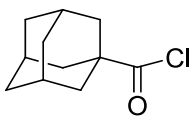
(*R*)-6-(2',2'-Dimethylpropionylamino)-[1,4]-thiazepan-5-one (**2.104**)



To **2.103** (100 mg, 0.44 mmol) and sodium carbonate (140 mg, 1.32 mmol) in a round bottomed flask was added 5 drops of H_2O. Trimethylacetylchloride (50 μL, 0.44 mmol) in dichloromethane (5 mL) was added to the solution and stirred at room temperature for 2 h. The organic layer was separated and the aqueous layer wash washed with copious amounts of dichloromethane. The organics were combined, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:1) to EtOAc (distilled solvents)) to give a white crystalline solid; (51 mg, 0.22 mmol, 50%); m.p.: 156-158 ^oC; $[\alpha]_D^{20}$ (c = 0.5, $CHCl_3$) -62.4; υ_{max} (cm^{-1}): 3389, 3282 (CONH), 2969 (CH_2 & CH_3), 1740, 1670, 1634 (CONH solid state & CONH lactam), 1493, 1465 (CH_2 & CH_3); δ_H (400 MHz, $CDCl_3$) 7.25-7.11 (2H, m, 2 × CON*H*), 4.85 (1H, ddd, *J* 8.5, 5.5, 2.5, CONHC*H*), 3.72-3.64 (2H, m, CONHCH_2), 2.78-2.69 (2H, m, CHCH_2S), 2.67 (1H, dd, *J* 10.0, 4.0, SC*H*HCH$_2$NH), 2.60 (1H, dt, *J* 14.5, 3.5, SCH*H*CH$_2$NH) and 1.27 (9H, s, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 177.9 (CH*C*ONH), 175.1 (*C*ONHCH), 55.6 (*C*HCONH), 45.6 (CONH*C*H$_2$), 38.7 (*C*(CH$_3$)$_3$) 30.9 (CHCH$_2$S*C*H$_2$), 30.6 (CH*C*H$_2$SCH$_2$) and 27.4 (C(*C*H$_3$)$_3$); *m/z* ($C_{10}H_{18}N_2NaO_2S$ (M + Na^+) requires 253.0981) found 253.0982. This compound has not previously been reported.

General Method F: Acid chloride synthesis from its carboxylic acid

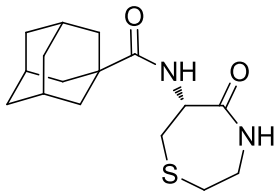
1-Adamantanecarbonyl chloride (**2.105** Synthon)



To a solution of 1-adamantanecarboxylic acid (1.0 g, 5.5 mmol) in dichloromethane (5.5 mL) was added oxalyl chloride (0.48 mL, 5.5 mmol) at 0 ^oC and a small drop of DMF. The solution was left stirring for 90 minutes, or

until completion following TLC, and concentrated *in vacuo* to give a white solid which was used immediately without further purification; (1.0 g, 5 mmol, 94%); m.p.: 51-52 ^{o}C; υ_{max} (cm^{-1}): 2905, 2852 (CH & CH_2), 1787 (COCl), 1689 (CO), 1452 (CH); δ_H (400 MHz, $CDCl_3$) 2.14-2.02 (3H, m, 3 × C*H*CH_2), 2.02-1.88 (6H, m, 3 × CHC*H*$_2$CH) and 1.80-1.65 (6H, m, 3 × CC*H*$_2$); δ_C (100 MHz, $CDCl_3$) 173.5 (*C*OCl), 38.6 (3 × *C*H_2 adamantane), 38.2 (*C*CO), 36.1 (3 × *C*H_2 adamantane), and 27.8 (3 × *C*H adamantane); *m/z* 221.1 (M + Na). This data is consistent with that previously reported.[319]

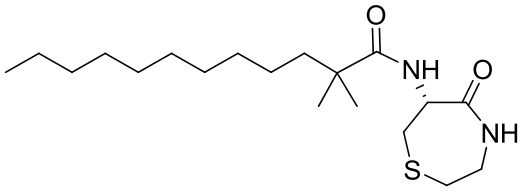
(*R*)-6-(1'-Adamantanecarbonylamino)-[1,4]-thiazepan-5-one (**2.105**)



Acylation was carried out according to **General Method E** using **2.103** (50 mg, 0.22 mmol) and adamantane-1-carbonyl chloride (44 mg, 0.22 mmol). The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:1) to EtOAc (distilled solvents)) to give a white crystalline solid; (62 mg, 20.1 mmol, 92%); m.p.: 237-240 ^{o}C; $[\alpha]_D^{21}$ (c = 1, $CHCl_3$) -15.45; υ_{max} (cm^{-1}) 3245 (CONH), 2905, 2848 (CH_2 & CH), 1682, 1660, 1630 (CONH solid state & CONH lactam), 1497, 1434 (CH_2); δ_H (400 MHz, $CDCl_3$) 7.16 (1H, d, *J* 5.0, N*H*CH), 6.20 (1H, t, *J* 6.0, N*H*CH_2), 4.88 (1H, ddd, *J* 9.5, 5.0, 2.0, NHC*H*CH_2), 3.77-3.76 (2H, m, NHC*H*$_2$CH$_2$) 2.77 (1H, d, *J* 14.5, SC*H*HCH_2) 2.73-2.65 (2H, m, CHC*H*$_2$S), 2.61 (1H, dd, *J* 14.5, 5.5, SCH*H*CH_2), 2.04 (3H, m, 3 × C*H*CH_2 adamantane), 1.90 (6H, d, *J* 2.5, 3 × CC*H*$_2$ adamantane) and 1.78-1.71 (6H, m, 3 × CHC*H*$_2$CH adamantane); δ_C (100 MHz, $CDCl_3$) 177.2 (CH*C*ONH), 175.0 (*C*ONHCH), 55.3 (CONH*C*H), 45.5 (CONH*C*H_2), 40.5 (*C*CO), 39.9 (3 × CH_2 adamantane), 36.3 (3 × CH_2 adamantane), 31.0 (CHCH_2S*C*H_2), 30.5

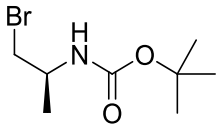
(CH*C*H_2SCH_2) and 27.9 (3 × CH adamantane); *m*/*z* ($C_{16}H_{24}N_2NaO_2S$ ($M + Na^+$) requires 331.1451) found 331.1444. This compound has not previously been reported.

(*R*)-6-(2',2'-Dimethyldodecanoylamino)-[1,4]-thiazepan-5-one (**2.106**)



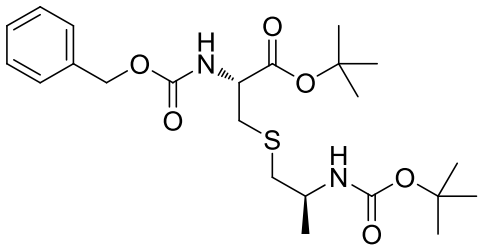
Acylation was carried out according to **General Method E** using **2.103** (50 mg, 0.2 mmol) and **2.138** (54 mg, 0.22 mmol). The residue was purified by silica column chromatography with distilled solvents (eluent; Petroleum Ether 40-60:EtOAc (1:1) to EtOAc) to give a clear viscous liquid (57 mg, 0.16 mmol, 72%); $[\alpha]_D^{29}$ (c = 0.1, MeOH) -5.0; υ_{max} (cm^{-1}) 3399, 3274 (CONH), 2921, 2852 (CH_2 & CH_3), 1638 (CONH lactam), 1467 (NH), 1409 (CH_3), 1354, 1321 ($C(CH_3)_2$), 721 (CH_2); δ_H (400 MHz, $CDCl_3$) 7.16 (1H, d, *J* 5.5, CON*H*CH), 6.73-6.58 (1H, m, CON*H*CH_2), 4.87 (1H, ddd, *J* 9.0, 5.5, 1.5, CONHC*H*), 3.77-3.60 (2H, m, NHC*H*$_2$), 2.77 (1H, d, *J* 14.0 NHCHC*H*HS), 2.72-2.64 (2H, m, CHCH*H*S & SC*H*HCH_2), 2.60 (1H, dd, *J* 14.5, 4.5, SCH*H*CH_2), 1.54-1.43 (2H, m, C*H*$_2$C$(CH_3)_2$), 1.25-1.22 (16H, m, CH_3(C*H*$_2$)$_8$), 1.16 (3H, s, C(C*H*$_3$)$_2$), 1.15 (3H, s, C(C*H*$_3$)$_2$) and 0.86 (3H, t, *J* 7.0, C*H*$_3$$CH_2$); δ_C (100 MHz, $CDCl_3$) 177.2 (*C*O), 174.9 (*C*O), 55.6 (CONH*C*H), 45.7 (NH*C*H_2), 42.1 (*C*$(CH_3)_2$), 41.3 (*C*H_2C$(CH_3)_2$), 31.8 (CH_3CH_2*C*H_2), 31.0, 30.6 (NHCH*C*H_2S & S*C*H_2CH_2), 30.1, 29.6, 29.53, 29.48, 29.3 ($CH_3CH_2CH_2$*C*H_2*C*H_2*C*H_2*C*H_2*C*H_2), 25.23 (C(*C*$H_3)_2$), 25.21 (C(*C*$H_3)_2$), 24.8 (*C*$H_2CH_2C(CH_3)_2$), 22.6 (CH_3*C*H_2) and 14.1 (*C*H_3CH_2); *m*/*z* ($C_{19}H_{36}N_2NaO_2S$ ($M + Na^+$) requires 379.2390) found 379.2390. This compound has not previously been reported.

(2*S*)-1-Bromo-2-*N*-*tert*-butoxycarbonylamino-propane (**(S)-2.107**)



Bromination was carried out according to **General Method G** using *N*-(*tert*-butoxycarbonylamino)-L-alaninol (1.8 g, 10.0 mmol). The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:1) to EtOAc) to give a clear viscous liquid (1.2 g, 5.0 mmol, 50%); $[\alpha]_D^{19}$ (c = 1, MeOH) -24.2; υ_{max} (cm^{-1}): 3317 (NH), 2975, 2933 (CH_3 &CH_2), 1685 (CO), 1499 (CH_2) 1159 (CO); δ_H (400 MHz, $CDCl_3$) 4.79-4.61 (1H, br s, NH), 3.95-3.79 (1H, m, C*H*CH_3), 3.53-3.33 (2H, m, BrCH_2), 1.38 (s, 9H, C(CH_3)$_3$) and 1.17 (3H, d, *J* 6.5, CHCH_3); δ_C (100 MHz, $CDCl_3$) 154.8 (*C*O), 46.1 (*C*HCH_3), 39.5 (Br*C*H_2), 28.2 (C(*C*H_3)$_3$) and 19.1 (*C*H_3CH); *m/z* ($C_8H_{16}BrNNaO_2$ ($M + Na^+$) requires 260.0257 and 262.0236) found 260.0261 and 262.0240. This compound is known but has previously been reported without any characterisation.[321]

2-Benzyloxycarbonylamino-3-(2-*tert*-butoxycarbonylamino-propylsulfanyl)-propionic acid *tert*-butyl ester (**(2*R*,2*S*)-2.108**)

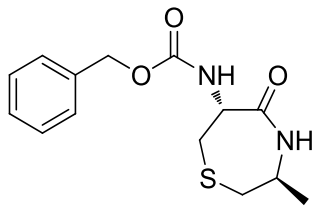


Coupling was carried out according to **General Method B** using **2.91** (1.2 g, 4.0 mmol) and **(*S*)-2.107** (1.0 g, 4.0 mmol). The crude product was purified by silica column chromatography (eluent; EtOAc:Hexane (1.5:8.5) to EtOAc) to give a colourless viscous liquid (0.6 g, 1.3 mmol, 33%); $[\alpha]_D^{26}$ (c = 0.5, MeOH) -18.6; υ_{max} (cm^{-1}) 3332 (CONH), 2975 & 2931 (CH Ph), 1702 (CONH), 1499 (NH),

1454 (CH_2), 1392 (CH_3), 1344 ($C(CH_3)_3$), 1240, 1152, 1044 (CO), 844 (CH_2), 775, 737 (*para*-Ph); δ_H (400 MHz, $CDCl_3$) 7.37-7.27 (5H, m, Ph), 5.79-5.65 (1H, br s, $PhCH_2OCONHCH$), 5.10 (2H, s, CH_2OCO), 4.77-4.65 (1H, br s, NHBoc), 4.49-4.40 (1H, m, $CHCOOC(CH_3)_3$), 3.89-3.68 (1H, m, $CHCH_3$), 2.98 (2H, d, *J* 5.0, $CH(COOC(CH_3)_3)CH_2S$), 2.62 (2H, d, *J* 5.0, SCH_2CHCH_3), 1.45 (9H, s, $C(CH_3)_3$), 1.41 (9H, s, $C(CH_3)_3$) and 1.13 (3H, d, *J* 6.5, CH_3CH); δ_C (100 MHz, $CDCl_3$) 169.6 ($CHCOOC(CH_3)_3$), 155.8 (OCONH), 155.2 (OCONH), 136.4 (*i*-Ph), 128.4 (Ph), 128.1 (Ph), 126.9 (*p*-Ph), 82.7 ($CHCOOC(CH_3)_3$), 79.3 ($NHCOOC(CH_3)_3$, 66.9 ($PhCH_2O$), 54.4 ($CHCOOC(CH_3)_3$), 46.1 ($CHCH_3$), 40.0 (SCH_2CHCH_3), 35.8 ($OCOCHCH_2S$), 28.3 ($C(CH_3)_3$), 27.9 ($C(CH_3)_3$) and 19.9 (CH_3CH); ESI *m/z* ($C_{23}H_{36}N_2NaO_6S$ (M + Na^+) requires 491.2186) found 491.2187, ($C_{18}H_{29}N_2O_4S$ (M – Boc + H^+) requires 369.1843) found 369.1843, ($C_{14}H_{21}N_2O_4S$ (M – Boc – ^tBu + H^+) requires 313.1217) found 313.1221. This compound has not previously been reported.

(3*S*,6*R*)-6-(Carboxybenzylamino)-3-methyl-[1,4]-thiazepan-5-one

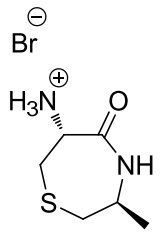
((3*S*,6*R*)-2.109)



Cyclisation was carried out according to **General Method C** using **(2*R*,2*S*)-2.108** (0.6 g, 1.2 mmol). The residue was purified by silica column chromatography (eluent; Petroleum Ether 40-60:EtOAc (9:1) to EtOAc) to give a white crystalline solid (0.2 g, 0.82 mmol, 64%); m.p.: 137-138 ^oC; $[\alpha]_D^{26}$ (c = 0.5, MeOH) +22.8; υ_{max} (cm^{-1}) 3284 (CONH), 2936 ($CH_, CH_2$), 1702, 1655 (CONH), 1491 (CH_3), 1452 (CH_2), 1350 ($COCH_2$), 1214 (CO), 728, 696 (*p*-Ph);

δ_H (400 MHz, $CDCl_3$) 7.37-7.26 (5H, m, Ph), 6.94 (1H, d, *J* 6.0, CON*H*CHCH$_3$), 6.32 (1H, d, *J* 5.5, CON*H*CHCONH), 5.09 (2H, s, PhC*H*$_2$OCO), 4.65-4.53 (1H, m, C*H*CONH), 3.90-3.75 (1H, m, C*H*CH$_3$), 2.94 (1H, d, *J* 14.0, *pseudo-eq.* CHC*H*HSCH$_2$CHCH$_3$), 2.76 (1H, d, *J* 14.5, *pseudo-eq.* CHCH$_2$SC*H*HCHCH$_3$), 2.64-2.55 (2H, m, *pseudo-ax.* CHCH*H*SCH*H*CH) and 1.37 (3H, d, *J* 6.5, CHC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 173.8 (CH*C*ONHCH), 155.4 (O*C*ONH), 136.2 (*i*-Ph), 128.5 (Ph), 128.1 (Ph), 126.7 (*p*-Ph), 67.1 (PhC*H*$_2$O), 57.3 (CONH*C*HCONH), 49.4 (*C*HCH$_3$), 36.8 (S*C*H$_2$CHCH$_3$), 30.5 (CH*C*H$_2$SCH$_2$CHCH$_3$) and 19.9 (*C*H$_3$); *m*/*z* ($C_{14}H_{18}N_2NaO_3S$ (M + Na^+) requires 317.0930) found 317.0938; This compound has not previously been reported.

(3*S*,6*R*)-6-(ammonium bromide)-3-methyl-[1,4]-thiazepan-5-one (**(3*S*,6*R*)-2.110**)

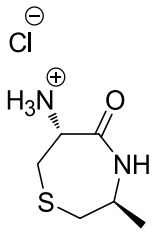


Deprotection was carried out according to **General Method D** using **(3*S*,6*R*)-2.109** (0.2 g, 0.7 mmol) to produce a viscous black liquid (0.2 g, 0.6 mmol, 92%); δ_H (400 MHz, MeOD) 4.12 (1H, dd, *J* 9.0, 4.5 C*H*$NH_3^+Br^-$), 3.58-3.50 (1H, m, C*H*CH$_3$), 2.74 (1H, dd, *J* 15.0, 3.0, *pseudo-eq.* SC*H*$_{eq}$HCHCH$_3$), 2.61-3.53 (2H, m, C*H*$_2$CH$NH_3^+Br^-$) 2.44 (1H, dd, *J* 15.0, 5.5, *pseudo-ax.* SCH*H*$_{ax}$CHCH$_3$) and 1.14 (3H, d, *J* 7.0, CHC*H*$_3$). δ_C (100 MHz, MeOD) 57.9 (*C*H$NH_3^+Br^-$), 49.3 (*C*HCH$_3$), 37.2 (S*C*H$_2$CHCH$_3$), 29.5 (*C*H$_2$CH$NH_3^+Br^-$) and 18.9 (*C*H$_3$). *m*/*z* ($C_6H_{13}N_2OS^+$ (M – Br^-) requires 161.0743) found 161.0746. This compound has not previously been reported.

Counter Ion Exchange (CIE)

(3*S*,6*R*)-6-(ammonium chloride)-3-methyl-[1,4]-thiazepan-5-one

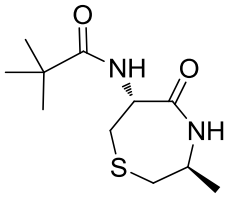
((3*S*,6*R*)-2.110CIE)



Compound **(3*S*,6*R*)-2.110** was stirred in 2 M methanolic HCl overnight. The resulting mixture was concentrated *in vacuo* to give the desired product as a white crystalline solid in quantitative yield; m.p. > 250 ^{o}C. Data was consistent with the above and the counter ion verified by mass spectrometry; *m*/*z* ($C_6H_{13}ClN_2NaOS$ (M + Na^+) requires 219.0335) found 219.0334, ($C_6H_{13}N_2OS^+$ (M – Cl^-) requires 161.0743) found 161.0745. This compound has not previously been reported.

(3*S*,6*R*)-6-(1'-dimethylpropionylamino)-3-benzyl-[1,4]-thiazepan-5-one

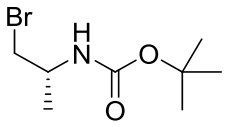
((3*S*,6*R*)-2.111)



Acylation was carried out according to **General Method E** using **(3*S*,6*R*)-2.110CIE** (82 mg, 0.4 mmol) and trimethylacetyl chloride (5 μL, 0.4 mmol). The residue was purified by silica column chromatography (eluent; Petroleum Ether 40-60:EtOAc (1:1) to EtOAc) to give a white crystalline solid (52 mg, 0.2 mmol, 51%); m.p.: 174-175 ^{o}C; $[\alpha]_D^{29}$ (c = 0.05, MeOH) +36.2; υ_{max} (cm^{-1}) 3386 (NH),

3283 (CONH), 2968, 2930, 2871 (CH, CH_2, CH_3) 1632 (CONH), 1363 ($C(CH_3)_3$), 1304, 1287 (CO); δ_H (400 MHz, $CDCl_3$) 7.19 (1H, d, *J* 4.0, $(CH_3)_3CCONHCH$), 6.28 (1H, d, *J* 7.0, $CONHCHCH_3$), 4.75 (1H, ddd, *J* 8.0, 5.5, 4.0, NHCHCONH), 3.85-3.74 (1H, m, $CHCH_3$), 2.94 (1H, dd, *J* 15.0, 2.5, *pseudo-eq.* $CHCHHSCH_2CHCH_3$), 2.92 (1H, ddd, *J* 14.0, 2.0, 1.0 *pseudo-eq.* $CHCH_2SCHHCHCH_3$), 2.66 (1H, ddd, *J* 15.0, 6.0, 1.0, *pseudo-ax.* $CHCHHSCH_2CHCH_3$), 2.57 (1H, dd, *J* 14.0, 10.0, *pseudo-ax.* $CHCH_2SCHHCHCH_3$), 1.50 (3H, d, *J* 7.0, $CHCH_3$) and 1.22 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 173.9 ($(CH_3)_3CCO$), 170.5 (CONHCH), 56.1 ($CONHCHCONH$), 49.5 ($CHCH_3$), 38.8 ($C(CH_3)_3$) 36.7 (SCH_2CHCH_3), 30.8 ($CHCH_2SCH_2CHCH_3$), 27.5 ($C(CH_3)_3$) and 19.2 ($CHCH_3$); *m/z* ($C_{11}H_{20}N_2NaO_2S$ ($M + Na^+$) requires 267.1138) found 267.1132; This compound has not previously been reported.

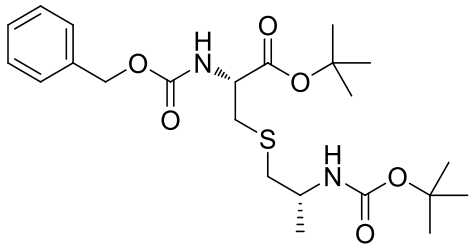
(2*R*)-1-Bromo-2-*N*-*tert*-butoxycarbonylamino-propane (**(*R*)-2.107**)



Bromination was carried out according to **General Method G** using *N*-*tert*-butoxycarbonylamino-D-alaninol (0.5 g, 2.8 mmol). The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:1) to EtOAc) to give an off white crystalline product (0.4 g, 1.7 mmol, 60%); m.p.: 86-88 ^oC; $[\alpha]_D^{19}$ (c = 1, MeOH) +22.8; υ_{max} (cm^{-1}): 3315 (NH), 2975, 2934 (CH_3 & CH_2), 1690 (CO), 1159 (CO); δ_H (400 MHz, $CDCl_3$) 4.87 (1H, d, *J* 8.0, NH), 3.91-3.72 (1H, m, $CHCH_3$), 3.41-3.33 (2H, m, $BrCH_2$), 1.33 (s, 9H, $C(CH_3)_3$) and 1.13 (3H, d, *J* 6.5, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 154.6 (CO), 79.9 ($C(CH_3)_3$), 45.4 ($CHCH_3$), 39.4 ($BrCH_2$), 28.2 ($C(CH_3)_3$) and 19.1 (CH_3CH); HR ESI *m/z* ($C_8H_{16}BrNNaO_2$ ($M + Na^+$) requires 260.0257 and 262.0236) found 260.0258 and 262.0238. This

compound is known but has previously only been reported with ^{1}H NMR spectroscopic data, which is consistent with that reported here.[322]

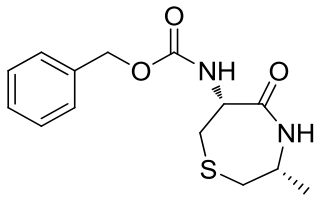
2-Benzyloxycarbonylamino-3-(2-*tert*-butoxycarbonylamino-propylsulfanyl)-propionic acid *tert*-butyl ester (**(2*R*,2*R*)-2.108**)



Coupling was carried out according to **General Method B** using **2.91** (0.53 g, 1.7 mmol) and **(*R*)-2.107** (0.4 g, 1.7 mmol). The crude product was purified by silica column chromatography (eluent; EtOAc:Hexane (1:9) to EtOAc) to give a viscous liquid (0.4 g, 0.9 mmol, 49%); $[\alpha]_D^{24}$ (c = 1, MeOH) -21.9; υ_{max} (cm^{-1}) 3343 (CONH), 2976 & 2932 (CH Ph), 1697 (CONH), 1499 (NH), 1454 (CH_2), 1392 (CH_3), 1344 ($C(CH_3)_3$), 1244, 1152 (CO), 843 (CH_2), 774, 731 (*p*-Ph); δ_H (400 MHz, $CDCl_3$) 7.36-7.24 (5H, m, Ph), 5.73 (1H, d, *J* 6.5, $CH_2OCONHCH$), 5.09 (2H, s, CH_2OCO), 4.81-4.61 (1H, br s, $NHCOOC(CH_3)_3$), 4.45 (1H, dd, *J* 13.0, 5.5, $CHCOOC(CH_3)_3$), 3.86-3.66 (1H, m, $CHCH_3$), 3.00 (1H, dd, *J* 13.5, 4.5, $CHCHHSCH_2CHCH_3$), 2.93 (1H, dd, *J* 13.5, 5.5, $CHCHHSCH_2CHCH_3$), 2.68 (1H, dd, *J* 13.0, 5.5, $SCHHCHCH_3$), 2.54 (1H, dd, *J* 13.0, 6.0, $SCHHCHCH_3$), 1.45 (9H, s, $C(CH_3)_3$), 1.40 (9H, s, $C(CH_3)_3$) and 1.12 (3H, d, *J* 6.5, CH_3CH); δ_C (100 MHz, $CDCl_3$) 169.5 ($CHCOOC(CH_3)_3$), 155.6 (OCONH), 155.0 (OCONH), 136.2 (*i*-Ph), 128.33 (Ph), 128.32 (Ph), 127.9 (*p*-Ph), 82.5 ($C(CH_3)_3$), 66.8 ($PhCH_2O$), 54.3 ($CHCO_2{}^tBu$), 45.9 ($CHCH_3$), 39.6 (SCH_2CHCH_3), 35.4 ($OCOCHCH_2S$), 28.3 ($C(CH_3)_3$), 27.8 ($C(CH_3)_3$) and 19.8 (CH_3CH); *m*/*z* ($C_{23}H_{36}N_2NaO_6S$ (M + Na^+) requires 491.2186) found 491.2176. This compound has not previously been reported.

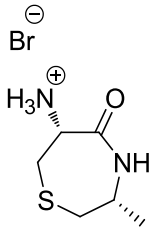
(3*R*,6*R*)-6-(Carboxybenzylamino)-3-methyl-[1,4]-thiazepan-5-one

((3*R*,6*R*)-2.109)



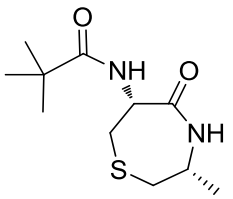
Cyclisation was carried out according to **General Method C** using **(2*R*,2'*R*)-2.108** (0.4 g, 0.85 mmol). The residue was purified by silica column chromatography (eluent; Hexane:EtOAc (8:2) to EtOAc) to give a white crystalline solid (0.12 g, 0.42 mmol, 49 %); m.p.: 127-128 ^{o}C; $[\alpha]_D^{29}$ (c = 0.5, MeOH) -45.5; υ_{max} (cm^{-1}) 3399, 3307 (CONH), 3060, 2965, 2901 (CH, CH_2), 1726, 1699 (CONH), 1655 (CO), 1489 (CH_3), 1435 (CH_2), 1344 ($COCH_2$), 1233, 1208 (CO), 754, 729, 695 (*p*-Ph); δ_H (400 MHz, $CDCl_3$) 7.41-7.28 (5H, m, Ph), 6.61 (1H, d, *J* 5.0, N*H*CHCH$_3$), 6.30 (1H, d, *J* 5.5, PhCH$_2$OCON*H*), 5.12 (1H, d, *J* 12.5, PhC*H*HOCO), 5.09 (1H, d, *J* 12.5, PhCH*H*OCO), 4.78-4.70 (1H, m, C*H*CONH), 3.94-3.85 (1H, m, C*H*CH$_3$), 2.82 (1H, d, *J* 14.0, CHC*H*HSCH$_2$CHCH$_3$), 2.73 (1H, dd, *J* 14.0, 9.5, CHCH*H*SCH$_2$CHCH$_3$), 2.56 (1H, dd, *J* 14.5, 9.0, CHCH$_2$SC*H*HCHCH$_3$), 2.46 (1H, dd, *J* 14.5, CHCH$_2$SCH*H*CHCH$_3$), and 1.30 (3H, d, *J* 6.5, CHC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 173.2 (CH*C*ONHCH), 155.1 (O*C*ONH), 136.2 (*i*-Ph), 128.4 (Ph), 128.1 (Ph), 128.0 (Ph), 66.8 (PhCH$_2$O), 57.0 (CONH*C*HCONH), 53.0 (*C*HCH$_3$), 36.8 (S*C*H$_2$CHCH$_3$), 31.0 (CH*C*H$_2$SCH$_2$CHCH$_3$) and 22.0 (*C*H$_3$); *m*/*z* ($C_{14}H_{18}N_2NaO_3S$ (M + Na^+) requires 317.0930) found 317.0932. This compound has not previously been reported.

(3*R*,6*R*)-6-(ammonium bromide)-3-methyl-[1,4]-thiazepan-5-one (**(3*R*,6*R*)-2.110**)



Deprotection was carried out according to **General Method D** using **(3*R*,6*R*)-2.109** (124 mg, 0.42 mmol) to give an off white solid (96 mg, 0.40 mmol, 95%); m.p.: >250 ^{o}C; $[\alpha]_D^{24}$ (c = 0.5, MeOH) -3.1; υ_{max} (cm^{-1}) 3205 (CONH), 2975, 2903 (CH, CH_2), 1649 (CONH), 1596 (NH_3^+), 1484 (CH_3), 1450 (CH_2); δ_H (400 MHz, MeOD) 4.52 (1H, dd, *J* 9.0, 3.0 C*H*$NH_3^+Br^-$), 3.91-3.82 (1H, m, C*H*CH_3), 2.85 (1H, dd, *J* 14.5, 9.0, *pseudo-ax.* SCH*H*CH$NH_3^+Br^-$), 2.76 (1H, dd, *J* 14.5, 3.0, *pseudo-eq.* SC*H*HCH$NH_3^+Br^-$), 2.62 (1H, dd, *J* 14.5, 1.0, *pseudo-eq.* SC*H*HCHCH_3), 2.54 (1H, dd, *J* 14.5, 9.0, *pseudo-ax.* SCH*H*CHCH_3) and 1.27 (3H, d, *J* 7.0, CHC*H*$_3$); δ_C (100 MHz, MeOD) 171.3 (*C*O), 57.1 (*C*H$NH_3^+Br^-$), 49.4 (*C*HCH_3), 37.7 (S*C*H_2CHCH_3), 28.5 (*C*H_2CH$NH_3^+Br^-$) and 21.4 (*C*H_3); *m*/*z* ($C_6H_{13}N_2OS^+$ (M – Br^-) requires 161.0743) found 161.0742. This compound has not previously been reported.

(3*R*,6*R*)-6-(1'-Dimethylpropionylamino)-3-benzyl-[1,4]-thiazepan-5-one (**(3*R*,6*R*)-2.111**)

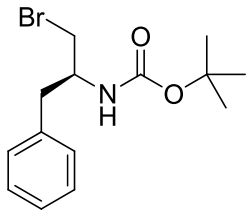


Acylation was carried out according to **General Method E** using **(3*R*,6*R*)-2.110** (24 mg, 0.1 mmol) and trimethylacetyl chloride (12 μL, 0.1 mmol, 1 eq). The

residue was purified by silica column chromatography (eluent; EtOAc:Petroleum Ether 40-60 (2:8) to EtOAc:Petroleum Ether 40-60 (1:1)) to give a white crystalline solid (21 mg, 0.1 mmol, 86%); m.p.: 138-139 ^{o}C; $[\alpha]_D^{30}$ (c = 0.072, MeOH) -41.9; υ_{max} (cm^{-1}) 3422 (NH), 3373, 3207 (CONH), 3085, 2959, 2904 (CH, CH_2, CH_3) 1673, 1644 (CONH), 1490 ($C(CH_3)_3$); δ_H (400 MHz, $CDCl_3$) 7.19 (1H, d, *J* 4.5, $(CH_3)_3CCONHCH$), 5.90 (1H, d, *J* 5.0, $CONHCHCH_3$), 4.85 (1H, ddd, *J* 8.0, 5.5, 2.0, $NHCHCONH$), 4.01-3.90 (1H, m, $CHCH_3$), 2.78 (1H, ddd, *J* 14.0, 2.0 1.0, *pseudo-eq.* $CHCHHSCH_2CHCH_3$), 2.66 (1H, dd, *J* 14.0, 9.5, *pseudo-ax.* $CHCHHSCH_2CHCH_3$), 2.59 (1H, dd, *J* 14.5, 9.0 *pseudo-ax.* $CHCH_2SCHHCHCH_3$), 2.50 (1H, dt, *J* 14.5, 1.0, *pseudo-eq.* $CHCH_2SCHHCHCH_3$), 1.33 (3H, d, *J* 7.0, $CHCH_3$) and 1.20 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 177.8 ($(CH_3)_3CCO$), 173.7 ($CONHCH$), 55.8 ($CONHCHCONH$), 53.1 ($CHCH_3$), 38.7 ($C(CH_3)_3$) 37.1 (SCH_2CHCH_3), 30.8 ($CHCH_2SCH_2CHCH_3$), 27.4 ($C(CH_3)_3$) and 22.3 ($CHCH_3$); *m/z* ($C_{11}H_{21}N_2O_2S$ ($M + H^+$) requires 245.1318) found 245.1317; This compound has not previously been reported.

General Method G: Alcohol bromination using NBS

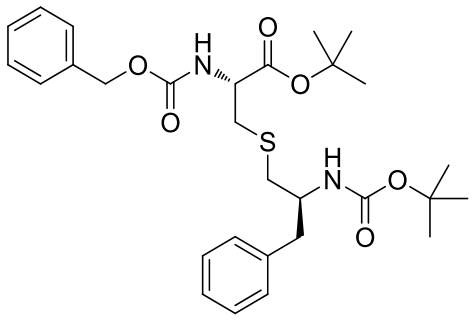
2,2-Benzyl-(*tert*-butyloxycarbonyl)amino-1-bromoethane (**(*S*)-2.112**)



N-Boc-L-phenylalaninol (5.0 g, 19.9 mmol) was dissolved in dry THF (75 mL) and triphenylphosphine (6.4 g, 24.5 mmol) was added in 3 portions with stirring. After complete addition, *N*-bromosuccinimide (4.3 g, 23.9 mmol) was added in 3 portions and allowed to stir on ice under nitrogen for 1 h after which time the

mixture was brought to room temperature and stirred for 16 h. The solution was filtered through a thin pad of celite© using 100 mL of EtOAc:Petroleum ether 40-60 (1:9) followed by 100 mL of EtOAc:Petroleum ether 40-60 (2:8) and concentrated *in vacuo*. The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:9) to EtOAc) to give a white crystalline solid (4.9 g, 15.8 mmol, 79%); m.p.: 100-102 ^{o}C; $[\alpha]_D^{19}$ (c = 1, MeOH) -1.12; υ_{max} (cm^{-1}) 3353 (CONH), 2974 (CH_2), 2929 (aryl CH) 1690, 1523 (CO), 1365, 1355 ($C(CH_3)_3$), 1266, 1251, 1163 (CO), 774, 703 (monosubstituted Ph), 654 (CBr); δ_H (400 MHz, $CDCl_3$) 7.35-7.20 (5H, m, Ph), 4.80 (1H, d, *J* 7.5, N*H*CH), 4.13-3.95 (1H, m, C*H*CH_2Br), 3.53 (1H, dd, *J* 10.0, 4.0, BrC*H*H), 3.36 (1H, dd, *J* 10.0, 3.5, BrCH*H*), 2.94 (1H, dd, *J* 13.5, 6.0, PhC*H*H) and 2.85 (1H, dd, *J* 13.5, 8.5, PhCH*H*), 1.42 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 129.3 (Ph), 128.7 (Ph), 126.9 (Ph), 51.5 (*C*HCH_2Br), 38.9 (Ph*C*H_2), 37.4 (Br*C*H_2) and 28.4 (CH_3); *m*/*z* ($C_{14}H_{20}{}^{79}BrNNaO_2$ (M + Na^+) requires 336.0570) found 336.0569. This compound is known but has previously only been reported with ^{1}H & ^{13}C NMR spectroscopic data, which is consistent with that reported here.[320]

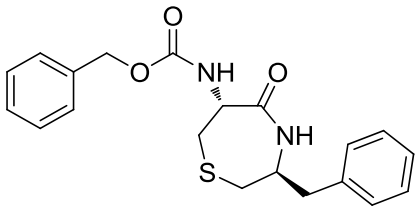
2-Benzyloxycarbonylamino-3-(2-*tert*-butoxycarbonylamino-3-phenyl-propylsulfanyl)-propionic acid *tert*-butyl ester (**(2*R*,2'*S*)-2.113**)



Coupling was carried out according to **General Method B** using **2.91** (0.6 g, 2.0 mmol) and **(*S*)-2.112** (0.6 g, 2.0 mmol). The residue was purified by silica

column chromatography (eluent; EtOAc:Hexane (1:9) to EtOAc) to give an off white crystalline solid (0.8 g, 1.5 mmol, 76%); m.p.: 82-83 ^{o}C; $[\alpha]_D^{22}$ (c = 1, MeOH) -6.5; υ_{max} (cm^{-1}) 3372 (CONH), 2979 (CH's, Ph), 1697, 1684 (CONH), 1518 (Ph), 1348 ($C(CH_3)_3$), 1211, 1158 (CO), 853 (CH), 734, 696 (*p*-Ph); δ_H (400 MHz, $CDCl_3$) 7.43-7.26 (5H, m, Ph), 7.26-7.16 (5H, m, Ph), 5.81 (1H, m, $PhCH_2OCONHCH$), 5.14 (2H, s, CH_2OCO), 4.90 (1H, m, $NHCHCH_2Ph$), 4.55-4.40 (1H, m, $CHCOOC(CH_3)_3$), 4.01-3.84 (1H, m, $CHCH_2Ph$), 3.05-2.93 (2H, m, $CHCH_2SCH_2CHCH_2Ph$), 2.92-2.76 (2H, m, SCH_2CHCH_2Ph), 2.74-2.56 (2H, m, SCH_2CHCH_2Ph), 1.48 (9H, s, $C(CH_3)_3$) and 1.43 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 169.6 ($CHCOOC(CH_3)_3$), 155.9 ($OCONH$), 155.3 ($OCONH$), 137.6 (*i*-Ph), 136.4 (*i*-Ph), 129.4 (Ph), 128.5 (Ph), 128.1 (Ph), 126.6 (Ph), 82.7 ($CHCOOC(CH_3)_3$), 79.4 ($NHCOOC(CH_3)_3$, 67.0 (CH_2OCO), 54.4 ($CONHCHCO$), 51.3 ($CHCH_2Ph$), 39.4 ($PhCH_2CH$), 37.3 ($PhCH_2CHCH_2S$), 35.9 ($OCOCHCH_2S$), 28.4 and 28.0 ($2 \times CH_3$); *m*/*z* ($C_{29}H_{40}N_2NaO_6S$ ($M + Na^+$) requires 567.2499) found 567.2507; anal. (CHN) ($C_{29}H_{40}N_2O_6S$ requires C 63.95, H 7.40, N 5.14) found C 63.94, H 7.39, N 4.97. This compound has not previously been reported.

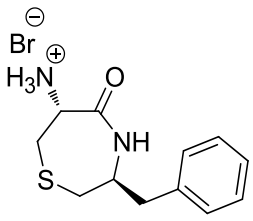
(3*S*,6*R*)-6-(Carboxybenzylamino)-3-benzyl-[1,4]-thiazepan-5-one (**(3*S*,6*R*)-2.114**)



Cyclisation was carried out according to **General Method C** using **(2*R*,2'*S*)-2.113** (1.7 g, 3 mmol). The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:1) to EtOAc) to give a white

crystalline solid (0.7 g, 1.8 mmol, 60%); m.p.: 53-54 ^{o}C; $[\alpha]_D^{19}$ (c = 1, MeOH) -58.7; υ_{max} (cm^{-1}) 3279 (CONH), 3031, 2922 (CH's, Ph), 1709, 1655 (CONH), 1494, 1452 (Ph), 1351 ($COCH_2$), 1213, 1050 (CO), 738, 696 (*p*-Ph); δ_H (400 MHz, $CDCl_3$) 7.46-7.35 (5H, m, Ph), 7.33-7.16 (5H, m, Ph), 6.28 (1H, d, *J* 5.0, CON*H*CHCONH), 6.14 (1H, d, *J* 6.5, CON*H*CH_2Ph), 5.16 (1H, d, *J* 13.5, PhC*H*HOCO), 5.13 (1H, d, *J* 13.5, PhCH*H*OCO), 4.79-4.69 (1H, m, C*H*CONH), 3.85-3.74 (1H, m, C*H*CH_2Ph), 3.28 (1H, dd, *J* 13.5, 8.5, CHC*H*HPh), 3.11 (1H, dd, *J* 13.5, 7.0, CHCH*H*Ph), 3.03 (1H, d, *J* 13.5, *pseudo-eq*. CHC*H*HSCH_2CHCH_2Ph), 2.88 (1H, d, *J* 14.5, *pseudo-eq*. $CHCH_2$SC*H*HCHCH_2Ph) and 2.69-2.61 (2H, m, *pseudo-ax*. CHCH*H*SCH*H*CHCH_2Ph); δ_C (100 MHz, $CDCl_3$) 173.8 (CH*C*ONHCH), 155.4 (O*C*ONH), 137.6 (*i*-Ph), 136.4 (*i*-Ph), 129.5 (Ph), 129.3 (Ph), 128.8 (Ph), 128.7 (Ph), 128.3 (Ph), 127.7 (Ph), 127.0 (Ph), 67.0 (Ph*C*H_2OCO), 57.7 (CONH*C*HCONH), 55.3 (PhCH_2*C*HNH), 38.9 (CH*C*H_2Ph), 34.0 (S*C*H_2CHCH_2Ph) and 31.0 (CH*C*H_2SCH_2CHCH_2Ph); *m*/*z* ($C_{20}H_{22}N_2NaO_3S$ (M + Na^+) requires 393.1243) found 393.1243. This compound has not previously been reported.

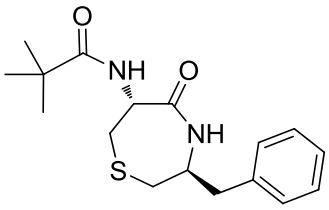
(3*S*,6*R*)-6-(ammonium bromide)-3-benzyl-[1,4]-thiazepan-5-one (**(3*S*,6*R*)-2.115)**



Deprotection was carried out according to **General Method D** using **(3*S*,6*R*)-2.114** (0.3 g, 0.7 mmol) to produce an orange solid (0.2 g, 0.5 mmol, 72%); m.p.: > 250 ^{o}C; υ_{max} (cm^{-1}) 3191 (CONH), 3095, 3004, 2919 (CH_2 & br, $Br^-NH_3^+$),

1656 (CONH lactam), 1594, 1553, 1500 (NH_3^+), 745 (Ph), 727 (CH_2S), 703 (Ph); δ_H (400 MHz, CD_3OD) 7.33-7.17 (5H, m, Ph), 4.55 (1H, dd, *J* 11.0, 2.0, $^+NH_3CHCH_2S$), 3.84 (1H, tdd, *J* 8.0, 5.0, 3.0, NHC*H*CH_2Ph), 3.21 (2H, d, *J* 8.0, NHCHC*H*$_2$Ph), 3.03 (1H, dd, *J* 15.0, 3.0, *pseudo-eq.* $CHCH_2SCHHCHCH_2Ph$), 2.92 (1H, dd, *J* 14.0, 11.0, *pseudo-ax.* $CHCHHSCH_2CHCH_2Ph$), 2.86-2.78 (1H, m, *pseudo-eq.* $CHCHHSCH_2CHCH_2Ph$) and 2.74 (1H, ddd, *J* 15.0, 5.0, 0.5 *pseudo-ax.* $CHCH_2SCHHCHCH_2Ph$); δ_C (100 MHz, CD_3OD) 136.6 (*i*-Ph) 130.4 (Ph), 129.8 (Ph), 127.9 (*p*-Ph), 58.3 ($NH_3CHCONH$), 55.8 ($PhCH_2CHNH$), 39.2 ($CHCH_2Ph$), 35.3 (SCH_2CHCH_2Ph) and 29.6 ($CHCH_2SCH_2CHCH_2Ph$); *m*/*z* ($C_{12}H_{17}N_2OS$ ($[M - Br]^+$) requires 237.1056) found 237.1054, ($C_{12}H_{14}NOS$ ($[M - NH_3Br]^+$) requires 220.0791) found 220.0791, ($C_{24}H_{32}N_4NaO_2S_2$ (2 × (M – HBr) + Na^+) requires 495.1864) found 495.1866. This compound has not previously been reported.

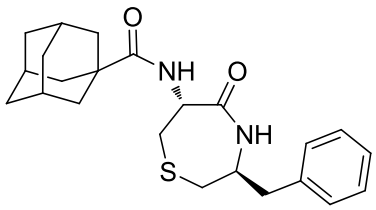
(3*S*,6*R*)-6-(2',2'-Dimethylpropionylamino)-3-benzyl-[1,4]-thiazepan-5-one **((3*S*,6*R*)-2.116)**



Acylation was carried out according to **General Method E** using **(3*S*,6*R*)-2.115** (25 mg, 0.08 mmol). The residue was purified by silica column chromatography with distilled solvents (eluent; EtOAc:Petroleum Ether 40-60 (1:1) to EtOAc) to give a white crystalline solid (19 mg, 0.06 mmol, 74%); m.p.: 122-123 ^oC; υ_{max} (cm^{-1}) 3379, 3358, 3248 (CONH), 2958 (CH_2), 1666 (CONH lactam), 1632 (CO), 1480 (NH), 1362 ($C(CH_3)_3$), 1293, 1271, 1227 (CO), 770 (Ph), 738 (CH_2S), 701 (Ph); δ_H (400 MHz, $CDCl_3$) 7.36-7.17 (6H, m, 5 × Ph &

CON*H*CHCONH) 6.43 (1H, d, *J* 7.5, N*H*CHCH$_2$Ph), 4.86 (1H, ddd, *J* 10.0, 5.5, 2.5, (CH$_3$)$_3$CCONHC*H*), 3.84-3.73 (1H, m, NHC*H*CH$_2$Ph), 3.37 (1H, dd, *J* 13.5, 8.5, NHCHC*H*HPh), 3.13 (1H, dd, *J* 13.5, 7.0, NHCHCH*H*Ph), 2.99 (1H, d, *J* 13.5 *pseudo-eq*. CHC*H*HSCH$_2$CHCH$_2$Ph), 2.90 (1H, dd, *J* 15.0, 3.0, *pseudo-eq*. SC*H*HCHCH$_2$Ph), 2.69 (1H, dd, *J* 15.0, 5.5, *pseudo*-ax. SCH*H*CHCH$_2$Ph), 2.58 (1H, dd, *J* 13.5, 10.0, *pseudo-ax*. CHCH*H*SCH$_2$CHCH$_2$Ph) and 1.25 (9H, s, C(C*H*$_3$)$_3$); δ_C (100 MHz, CDCl$_3$) 177.8 (CO), 173.9 (CO), 137.4 (*i*-Ph), 129.1 (Ph), 128.8 (Ph), 126.9 (*p*-Ph), 56.2 ((CH$_3$)$_3$CCONHC*H*), 55.8 (PhCH$_2$*C*HNH), 38.8 ((CH$_3$)$_3$*C*), 38.7 (CH*C*H$_2$Ph), 34.0 (S*C*H$_2$CHCH$_2$Ph), 30.8 (CH*C*H$_2$SCH$_2$CHCH$_2$Ph) and 27.4 (C(*C*H$_3$)$_3$); *m*/*z* ($C_{17}H_{24}N_2NaOS$ (M + Na^+) requires 343.1451) found 343.1448. This compound has not previously been reported.

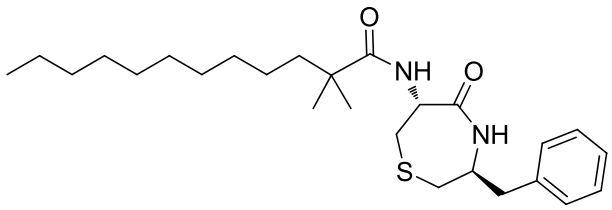
(3*S*,6*R*)-6-(1'-Adamantanecarbonylamino)-3-benzyl-[1,4]-thiazepan-5-one **((3*S*,6*R*)-2.117)**



Acylation was carried out according to **General Method E** using **(3*S*,6*R*)-2.115** (25 mg, 0.08 mmol). The residue was purified by silica column chromatography with distilled solvents (eluent; EtOAc to EtOAc:MeOH (9:1)) to give a white crystalline solid (11 mg, 0.03 mmol, 33%); m.p.: 97-98 ^oC; δ_H (400 MHz, CDCl$_3$) 7.33-7.15 (6H, m, Ph & CON*H*CHCONH), 6.24 (1H, d, *J* 7.5, N*H*CHCH$_2$Ph), 4.86 (1H, ddd, *J* 10.0, 5.5, 2.5, CCONHC*H*), 3.82-3.70 (1H, m, NHC*H*CH$_2$Ph), 3.35 (1H, dd, *J* 13.5, 8.0, NHCHC*H*HPh), 3.11 (1H, dd, *J* 13.5, 7.0, NHCHCH*H*Ph), 2.99 (1H, dd, *J* 14.0, 1.0 *pseudo-eq*.

CHC*H*HSCH$_2$CHCH$_2$Ph), 2.89 (1H, dd, *J* 15.0, 3.0, *pseudo-eq.* SC*H*HCHCH$_2$Ph), 2.68 (1H, dd, *J* 15.0, 5.5, *pseudo-ax.* SCH*H*CHCH$_2$Ph), 2.56 (1H, dd, *J* 14.0, 10.0, *pseudo-ax.* CHCH*H*SCH$_2$CHCH$_2$Ph), 2.06 (3H, m, 3 × C*H*CH$_2$ adamantane), 1.89 (6H, d, *J* 2.5, 3 × C(C*H$_2$*) adamantane) and 1.79-1.67 (6H, m, 3 × CHC*H$_2$*CH adamantane); δ_C (100 MHz, CDCl$_3$) 177.3 (*C*O), 173.9 (*C*O), 137.4 (*i*-Ph), 129.1 (Ph), 128.8 (Ph), 126.9 (*p*-Ph), 56.00 ((C)CONH*C*H), 55.96 (PhCH$_2$*C*HNH), 39.14 (3 × CH$_2$ adamantane), 39.12 (CH*C*H$_2$Ph), 37.1 ((*C*)CONH), 36.5 (3 × CH$_2$ adamantane), 34.1 (S*C*H$_2$CHCH$_2$Ph), 30.9 (CH*C*H$_2$SCH$_2$CHCH$_2$Ph) and 28.1 (3 × CH adamantane); *m*/*z* ($C_{23}H_{30}N_2NaO_2S$ (M + Na^+) requires 421.1920) found 421.1920, ($C_{12}H_{15}NOS$ (M – adamantanecarboxamide) requires 221.1260) found 221.1261. This compound has not previously been reported.

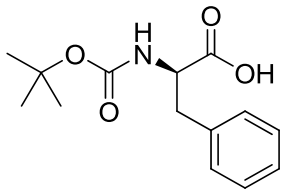
(3*S*, 6*R*)-6-(2',2'-Dimethyldodecanoylamino)-3-benzyl-[1,4]-thiazepan-5-one (**(3*S*, 6*R*)-2.118**)



Acylation was carried out according to **General Method E** using **(3*S*,6*R*)-2.115** (25 mg, 0.08 mmol) and **2.138** (20 mg, 0.08 mmol). The residue was purified by silica column chromatography with distilled solvents (eluent: 1:1 EtOAc:Petroleum Ether 40-60 to EtOAc) to give a white crystalline solid. (23 mg, 0.05 mmol, 65%); υ_{max} (cm^{-1}) 3393, 3238 (CONH), 2922, 2852 (CH$_2$, CH$_3$), 1641 (CONH lactam), 1476 (NH), 1356 (C(CH$_3$)$_2$), 1299 (CO), 740, 699 (Ph); δ_H (400 MHz, CDCl$_3$) 7.30-7.13 (6H, m, Ph + CON*H*CHCONH), 6.30 (1H, d, *J* 7.5, N*H*CHCH$_2$Ph), 4.84 (1H, ddd, *J* 10.5, 5.5, 2.5, CONHC*H*CONH), 3.73 (ddt,

1H, *J* 15.0, 8.0, 2.0, NHC*H*CH_2Ph), 3.32 (1H, dd, *J* 13.5, 8.0, NHCHC*H*HPh), 3.10 (1H, dd, *J* 13.5, 7.0, NHCHCH*H*Ph), 2.96 (1H, br d, *J* 14.0 *pseudo-eq*. CHC*H*HSCH_2CHCH_2Ph), 2.86 (1H, dd, *J* 15.0, 2.0, *pseudo-eq*. SC*H*HCHCH_2Ph), 2.64 (1H, dd, *J* 15.0, 5.5, *pseudo*-ax. SCH*H*CHCH_2Ph), 2.53 (1H, dd, *J* 14.0, 10.5, *pseudo-ax*. CHCH*H*SCH_2CHCH_2Ph), 1.54-1.42 (2H, m, CH_2C$(CH_3)_2$), 1.29-1.17 (16H, m, CH_3(C$H_2)_8$), 1.16 (3H, s, C(C$H_3)_2$), 1.15 (3H, s, C(C$H_3)_2$) and 0.84 (3H, t, *J* 7.0, CH_3CH_2); δ_C (100 MHz, $CDCl_3$) 177.3 (*C*O), 173.9 (*CO*), 137.4 (*i*-Ph), 129.1 (Ph), 128.8 (Ph), 126.9 (*p*-Ph), 56.2 (CONH*C*HCONH), 55.9 (*C*HCH_2Ph), 42.1 (*C*$(CH_3)_2$), 41.3 (*C*H_2C$(CH_3)_2$), 38.8 (*C*H_2Ph), 34.0 (S*C*H_2CHCH_2Ph), 31.9 (CH_3CH_2*C*H_2), 30.8 (NHCH*C*H_2SCH_2CHCH_2Ph), 30.2, 29.62, 29.58, 29.5, 29.3 ($CH_3CH_2CH_2$*C*H_2*C*H_2*C*H_2*C*H_2*C*H_2), 25.2 (C(*C*$H_3)_2$), 24.8 (*C*H_2CH_2C$(CH_3)_2$), 22.7 (CH_3*C*H_2) and 14.1 (*C*H_3CH_2); *m*/*z* ($C_{26}H_{42}N_2NaO_2S$ (M + Na^+) requires 469.2859) found 469.2864. This compound has not previously been reported.

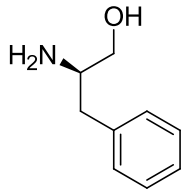
(*R*)-*N*-(*tert*-Butoxycarbonyl)-phenylalanine (**2.120**)



To a solution of D-phenylalanine (0.4 g, 2.7 mmol) in H_2O and NEt_3 (0.45 mL, 3.2 mmol) stirred at 0 ^oC was added a 0 ^oC solution of di-*tert*-butyl dicarbonate (0.7 g, 3.2 mmol) in THF. The mixture was stirred at 0 ^oC for 1 h and allowed to warm to room temperature overnight. The resulting solution was concentrated *in vacuo*, diluted with H_2O and acidified with 1M HCl. The aqueous mixture was extracted with ethyl acetate and the combined organic extracts washed with H_2O, sat. aq. NaCl, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (eluent; EtOAc:Petroleum Ether 40-60

(1:1) to EtOAc) to give a white crystalline solid (0.3 g, 1.3 mmol, 42%); m.p.: 86-87 ^{o}C; $[\alpha]_D^{19}$ (c = 1, MeOH) -9.7; υ_{max} (cm^{-1}) 3430 (NH), 3365, 3212 (CONH), 3085, 2961, 2903 (CH, CH_2, CH_3), 1676, 1642 (CONH), 1479 ($C(CH_3)_3$); δ_H (400 MHz, 2:1 rotamer ratio, $CDCl_3$) 8.32 (1H, br s, COO*H*), 7.34-7.14 (5H, m, Ph), ^{mi}6.44 (1H, d, *J* 7.0, N*H*), ^{mj}5.32 (1H, d, *J* 8.0, N*H*), ^{mj}4.68-4.63 (1H, m, C*H*), ^{mi}4.44-4.33 (1H, m, C*H*), 3.27-2.82 (2H, m, C*H*$_2$), ^{mj}1.42 (9H, s, C(C*H*$_3$)$_3$) and ^{mi}1.33 (9H, s, C(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 175.0 (*C*O), ^{mi}156.7 (*C*ONH), ^{mj}155.6 (*C*ONH), ^{mi}136.6 (*i*-Ph), ^{mj}136.3 (*i*-Ph), 129.5 (Ph), 128.5 (Ph), 126.9 (*p*-Ph), ^{mi}81.5 (*C*$(CH_3)_3$), ^{mj}80.1 (*C*$(CH_3)_3$), ^{mi}56.3 (*C*H), ^{mj}54.4 (*C*H), ^{mi}38.8 (*C*H_2), ^{mj}37.9 (*C*H_2), ^{mj}28.3 ($C(CH_3)_3$) and ^{mi}28.0 ($C(CH_3)_3$); *m*/*z* 266.1 ($M + H^+$) and 268 ($M + Na^+$). This data is consistent with that previously reported.[323]

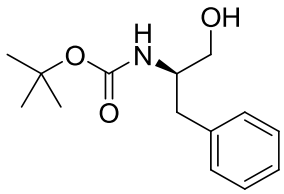
D-Phenylalaninol (**2.123**)



D-Phenylalanine (10.0 g, 60.5 mmol) was added to $NaBH_4$ (5.7 g, 151.3 mmol) in dry THF (80 mL) and cooled to 0 ^{o}C. A solution of H_2SO_4 (4.0 mL, 75.7 mmol) in diethyl ether (8 mL) was added dropwise at such a rate as to maintain the reaction temperature below 20 ^{o}C. Stirring of the reaction mixture was continued overnight at room temperature whereupon MeOH (6.05 mL) was added slowly followed by the slow addition of 5 M NaOH (61.75 mL, 308.7 mmol) until all solids were consumed. The MeOH and diethyl ether were removed by distillation and the remaining mixture refluxed overnight. After cooling the mixture was filtered through a thin pad of celite©, washed with H_2O, extracted using dichloromethane (3 × 50 mL) and concentrated *in vacuo*. The

crude product was recrystallised from ethyl acetate and hexane to give a white crystalline solid (5.6 g, 37 mmol, 61%); m.p.: 91-92 ^{o}C; $[\alpha]_D^{22}$ (c = 1, MeOH) +21.6; υ_{max} (cm^{-1}) 3432, 3334 (NH_2, OH), 2961, 2887 (CH, CH_2), 1561 (NH_2), 1127 (COH), 790, 729, 699 (Ph); δ_H (400 MHz, $CDCl_3$) 7.34-7.28 (2H, m, *o*-Ph), 7.23 (1H, dt, *J* 8.5, 1.5, *p*-Ph), 7.21-7.17 (2H, m, *m*-Ph), 3.63 (1H, dd, *J* 10.5, 4.0, C*H*HOH), 3.38 (1H, dd, *J* 10.5, 7.0, CH*H*OH), 3.12 (1H, dddd, *J* 10.5, 8.5, 5.5, 4.0, C*H*), 2.79 (1H, dd, *J* 13.5, 5.5, C*H*HC), 2.53 (1H, dd, *J* 13.5, 8.5, CH*H*C), 2.0-1.3 and (3H, br s, N*H*$_2$ & O*H*); δ_C (100 MHz, $CDCl_3$) 138.6 (*i*-Ph), 129.2 (Ph), 128.6 (Ph), 126.4 (*p*-Ph), 66.5 (*C*H_2OH), 54.1 (*C*H) and 41.1 (*C*H_2C); *m*/*z* 152.2 (M + H^+) and 174.1 (M + Na^+). This data is consistent with that previously reported.[324]

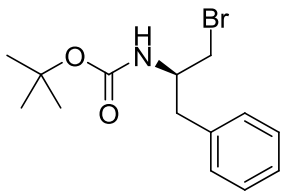
N-(*tert*-Butoxycarbonyl)-D-phenylalaninol (**2.122**)



Di-*tert*-butyl dicarbonate (2.2 g, 10 mmol) in dichloromethane (40 mL) was added dropwise to a solution of **2.123** (1.5 g, 10 mmol) in dichloromethane (40 mL) and 1 M NaOH (32 mL). The solution was stirred for 3 days at room temperature whereupon the organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 40 mL). The organics were combined, washed with H_2O (2 × 20 mL), over sodium sulfate and concentrated *in vacuo*. The residue was purified by silica column chromatography (eluent; EtOAc:Petroleum Ether 40-60 (1:9) to EtOAc:Petroleum Ether 40-60 (1:1)) to give a white crystalline solid (1.6 g, 6.4 mmol, 65.0%); m.p.: 102-103 ^{o}C; $[\alpha]_D^{28}$ (c = 0.16, MeOH) +28.4; υ_{max} (cm^{-1}) 3346 (NH), 3026 (CONH), 2983, 2937, 2875 (CH, CH_2, CH_3), 1684, 1603 (NH_2), 1526 (CONH), 1497, 1442 (C(CH_3)$_3$,

CH_2), 1365 (CH_3), 1314 (OH), 1269, 1250 (CO), 1166, 1004 (COH), 775, 754 (Ph), 737 (CH_2), 700 (Ph); δ_H (400 MHz, $CDCl_3$) 7.32-7.19 (5H, m, Ph), 5.04 (1H, br s, NH), 3.88 (1H, br s, CH), 3.63 (1H, dd, *J* 11.0, 4.0, C*H*$_2$OH), 3.54 (1H, dd, *J* 11.0, 5.0, C*H*$_2$OH), 3.38 (1H, br s, OH), 2.85 (2H, d, *J* 7.0, C*H*$_2$C) and 1.42 (9H, s, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 156.1 (CO), 137.9 (*i*-Ph), 129.2, 128.3 (*o*-, *m*-Ph), 126.3 (*p*-Ph), 79.5 (*C*(CH_3)$_3$), 63.6 (CH_2OH), 53.5 (CH), 37.3 (*C*H_2C) and 28.2 (C(*C*H_3)$_3$); *m*/*z* 100 %, 274.1 ([M + Na]$^+$) and 24 %, 524.8 ([(2 × M) – H + Na]$^+$). This data is consistent with that previously reported.[325]

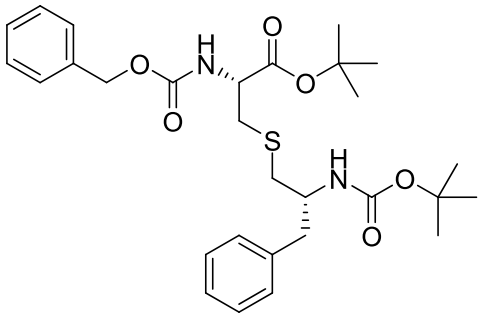
(*R*)-2-*tert*-butoxycarbonylamino-3-phenyl-1-propylbromide ((***R*)-2.112**)



Bromination was carried out according to **General Method G** using **2.122** (1.6 g, 6.5 mmol) and dichloromethane in place of THF. The residue was purified by silica column chromatography (eluent; EtOAc:Petroleum Ether 40-60 (1:9) to EtOAc:Petroleum Ether 40-60 (1:1)) to give an off white crystalline product (0.9 g, 2.8 mmol, 44%); m.p.: 101-102 ^oC; $[\alpha]_D^{22}$ (c = 1, MeOH) +5.4; υ_{max} (cm^{-1}): 3348 (CONH), 3064, 2974 (CH_2, CH_3), 2932 (C(CH_3)$_3$), 1690 (CONH), 1525 (CO), 1365, 1356 (CH_3), 1267, 1251 (CO), 1052, 1020 (COC), 773, 745, 703 (Ph), 653 (CBr); δ_H (400 MHz, $CDCl_3$) 7.35-7.23 (5H, m, Ph), 4.90 (1H, d, *J* 7.5 N*H*), 4.12-3.99 (1H, m, C*H*), 3.54 (1H, dd, *J* 10.5, 4.0, C*H*HBr), 3.37 (1H, dd, *J* 10.5, 3.5, CH*H*Br), 2.95 (1H, dd, *J* 13.5, 5.5, C*H*HC), 2.87 (1H, dd, *J* 13.5, 8.5, CH*H*C), and 1.46 (9H, s, C(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 154.8 (*C*O), 137.0 (*i*-Ph), 129.1 (Ph), 128.5 (Ph), 126.7 (*p*-Ph), 79.6 (*C*(CH_3)$_3$), 51.4 (*C*H), 38.7 (*C*H_2C), 37.2 (*C*H_2Br), and 28.2 (C(*C*H_3)$_3$); *m*/*z* ($C_{14}H_{20}BrNNaO_2$ (M + Na$^+$) requires 336.0570 & 338.0550) found 336.0566 and 338.0548. This compound is

known but has previously only been reported with ^{1}H & ^{13}C NMR spectroscopic data, which is consistent with that reported here.[326]

2-Benzyloxycarbonylamino-3-(2-*tert*-butoxycarbonylamino-3-phenyl-propylsulfanyl)-propionic acid *tert*-butyl ester (**(2*R*,2'R)-2.113**)

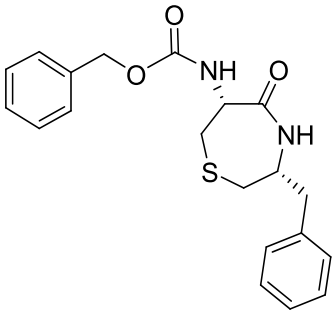


Coupling was carried out according to **General Method B** using **(*R*)-2.112** (0.9 g, 2.8 mmol) and **2.91** (0.9 g, 2.8 mmol). The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:9) to EtOAc:Hexane (1:1)) to give a white crystalline solid (0.4 g, 0.7 mmol, 25%); m.p.: 89-90 ^{o}C; $[\alpha]_D^{28}$ (c = 1, MeOH) -36.5; υ_{max} (cm^{-1}) 3369 (CONH), 2981 (CH), 1733 (COO), 1686 (CONH), 1503 (Ph), 1382, 1367, 1351 (CHs & $C(CH_3)_3$), 1211, 1156 (CO), 843 (CH_2), 774, 756, 696 (*p*-Ph); δ_H (400 MHz, $CDCl_3$) 7.38-7.16 (10H, m, Ph), 5.75 (1H, d, *J* 7.5, $PhCH_2OCONHCH$), 5.13 (2H, s, CH_2OCO), 4.85 (1H, dd, *J* 6.5, $NHCHCH_2Ph$,), 4.49 (1H, m, $CHCOOC(CH_3)_3$), 4.08-3.78 (1H, m, $CHCH_2Ph$), 3.04 (1H, dd, *J* 13.5, 4.5, $CHCHHSCH_2CHCH_2Ph$), 2.97 (1H, dd, *J* 13.5, 5.5, $CHCHHSCH_2CHCH_2Ph$) 2.92-2.76 (2H, m, SCH_2CHCH_2Ph), 2.74-2.56 (2H, m, SCH_2CHCH_2Ph), 1.49 (9H, s, $C(CH_3)_3$) and 1.43 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 169.4 ($CHCOOC(CH_3)_3$), 155.6 ($OCONH$), 155.0 ($OCONH$), 137.4 (*i*-Ph), 136.1 (*i*-Ph), 129.2 (Ph), 128.3 (Ph), 128.0 (Ph), 127.9 (Ph), 126.4 (*p*-Ph), 82.6 ($CHCOOC(CH_3)_3$), 79.2 ($NHCOOC(CH_3)_3$), 66.8 (CH_2OCO), 54.2 ($CONHCHCO$), 51.0 ($CHCH_2Ph$), 39.4 ($PhCH_2CH$), 36.8 ($PhCH_2CHCH_2S$), 35.4 ($OCOCHCH_2S$), 28.2 ($CHCOOC(CH_3)_3$) and 27.8 ($NHCOOC(CH_3)_3$); *m*/*z*

($C_{29}H_{40}N_2NaO_6S$ (M + Na^+) requires 567.2499) found 567.2495. This compound has not previously been reported.

(3*R*,6*R*)-6-(Carboxybenzylamino)-3-benzyl-[1,4]-thiazepan-5-one

((3*R*,6*R*)-2.114)

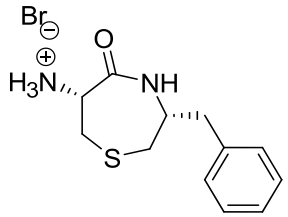


Cyclisation was carried out according to **General Method C** using **(2*R*,2'*R*)-2.113** (0.4 g, 0.7 mmol). The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (4:6) to EtOAc) to give a white crystalline solid (44 mg, 0.1 mmol, 17%); m.p.: 128-129 ^oC; $[\alpha]_D^{24}$ (c = 0.2, MeOH) +33.6; υ_{max} (cm^{-1}) 3406, 3223 (CONH), 3066, 2916 (CH's, Ph), 1726, 1713 (CO), 1670 (CONH lactam), 1483, 1452 (Ph), 1358 ($COCH_2$), 1213, 1058 (CO), 774, 741, 694 (Ph); δ_H (400 MHz, $CDCl_3$) 7.40-7.24 (8H, m, Ph), 7.20-7.14 (2H, m, 2 × *p*-Ph), 6.26 (1H, d, *J* 6.0, CON*H*CHCONH), 6.21 (1H, d, *J* 5.5, CON*H*CHCH_2Ph), 5.12 (1H, d, *J* 12.0, PhC*H*HOCO), 5.09 (1H, d, *J* 12.0, PhCH*H*OCO), 4.75 (1H, ddd, *J* 8.5, 6.0, 2.0, C*H*CONH), 4.11-4.03 (1H, m, C*H*CH_2Ph), 2.86 (2H, d, *J* 7.5, CHC*H*$_2$Ph), 2.85-2.79 (1H, m, *pseudo-eq.* SC*H*HCHCH_2Ph), 2.74 (1H, dd, *J* 14.0, 9.5, *pseudo-ax.* SCH*H*CHCH_2Ph), 2.61 (1H, dd, *J* 14.5, 2.0, *pseudo-eq.* CHC*H*HSCH_2CHCH_2Ph) and 2.56 (1H, dd, *J* 14.5, 8.5, *pseudo-ax.* CHCH*H*SCH_2CHCH_2Ph); δ_C (100 MHz, $CDCl_3$) 173.1 (CH*C*ONHCH), 155.2 (O*C*ONH), 136.2 (*i*-Ph), 135.7 (*i*-Ph), 129.12 (Ph), 129.11 (Ph) 128.5 (Ph), 128.1 (Ph), 128.0 (Ph), 127.4 (Ph), 66.9 (Ph*C*H_2OCO), 58.1 (*C*HCH_2Ph), 57.0 (CONH*C*HCONH), 41.8 (CH*C*H_2Ph), 34.9

(CH*C*H_2SCH_2CHCH_2Ph) and 31.2 (S*C*H_2CHCH_2Ph); *m*/*z* ($C_{20}H_{22}N_2NaO_3S$ (M + Na^+) requires 393.1243) found 393.1243. This compound has not previously been reported.

(3*R*,6*R*)-6-(ammonium bromide)-3-benzyl-[1,4]thiazepan-5-one

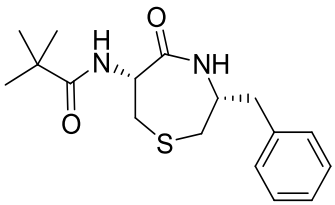
((3*R*,6*R*)-2.115))



Deprotection was carried out according to **General Method D** using (**3*R*,6*R***)-**2.114** (44 mg, 0.1 mmol) to produce a white crystalline solid (37 mg, 0.1 mmol, 99%); m.p.: > 250 ^oC; $[\alpha]_D^{28}$ (c = 0.57, MeOH) +58.8; υ_{max} (cm^{-1}) 3420, 3183 (CONH), 3084, 3002, 2823 (CH_2 & NH_3^+), 1642, 1638 (CONH lactam & NH_3^+), 1492 (NH_3^+), 772, 755, 707 (Ph); δ_H (400 MHz, CD_3OD) 7.34-7.20 (5H, m, Ph), 4.57 (1H, dd, *J* 9.0, 3.5, $^+NH_3C$*H*CH_2S), 4.05 (1H, dddd, *J* 9.5, 7.5, 6.0, 2.0, NHC*H*CH_2Ph), 2.96 (1H, dd, *J* 14.0, 7.5, *pseudo-ax.* NHCHCH*H*Ph), 2.89 (1H, dd, *J* 14.5, 9.0, *pseudo-ax.* COCHCH*H*SCH_2), 2.87 (1H, dd, *J* 14.0, 6.0, *pseudo-eq.* NHCHC*H*HPh), 2.80 (1H, dd, *J* 14.5, 3.5, *pseudo-eq.* COCHC*H*HSCH_2), 2.70 (1H, dd, *J* 14.0, 1.5, *pseudo-eq.* SC*H*HCHCH_2Ph) and 2.60 (1H, dd, *J*, 14.0, 9.5, *pseudo-ax.* SCH*H*CHCH_2Ph); δ_C (100 MHz, CD_3OD) 130.4 (Ph), 129.8 (Ph), 128.1 (Ph), 59.0 (PhCH_2*C*HNH), 56.8 (NH_3*C*HCONH), 41.8 (CH*C*H_2Ph), 35.8 (S*C*H_2CHCH_2Ph) and 28.7 (CH*C*H_2SCH_2CHCH_2Ph); *m*/*z* ($C_{12}H_{17}N_2OS$ (M – Br^-) requires 237.1056) found 237.1054. This compound has not previously been reported.

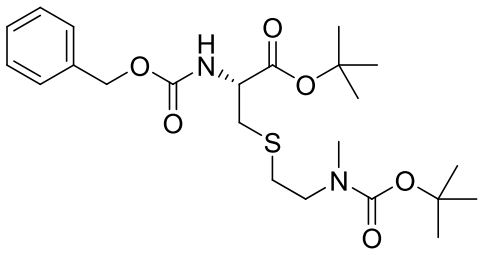
(3*R*,6*R*)-6-(2',2'-Dimethylpropionylamino)-3-benzyl-[1,4]-thiazepan-5-one

((3*R*,6*R*)-2.116))



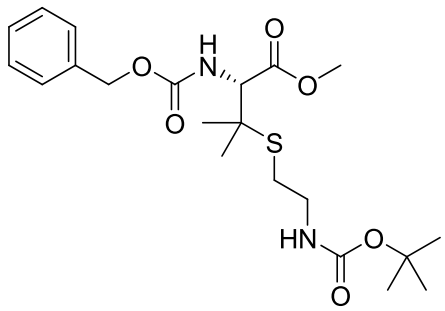
Acylation was carried out according to **General Method E** using (**3*R*,6*R***)-**2.115**), 13 mg, 0.04 mmol). The residue was purified by silica column chromatography (eluent; EtOAc (distilled)) to give a white crystalline solid (8 mg, 0.02 mmol, 61 %); m.p.: 228-229 ^{o}C; $[\alpha]_D^{19}$ (c = 0.16, MeOH) +19.7; υ_{max} (cm^{-1}) 3404, 3361 (CONH), 2956 (CH_2), 1641 (CONH lactam), 1632 (CO), 1491 (NH), 1361 ($C(CH_3)_3$), 1271, 1220 (CO), 772, 753, 701 (Ph); δ_H (400 MHz, $CDCl_3$) 7.37-7.27 (3H, m, Ph), 7.20-7.15 (3H, m, Ph & N*H*COC$(CH_3)_3$) 5.74 (1H, d, *J* 6.0, N*H*CHCH$_2$Ph), 4.85 (1H, ddd, *J* 9.5, 5.5, 2.5, $(CH_3)_3$CONHC*H*), 4.16-4.06 (1H, m, NHC*H*CH$_2$Ph), 2.92 (1H, dd, *J* 14.0, 7.0, NHCHC*H*HPh), 2.87-2.75 (2H, m, NHCHCH*H*Ph & CHC*H*HSCH$_2$CHCH$_2$Ph), 2.70-2.61 (2H, m, CHCH*H*SCH$_2$CHCH$_2$Ph & SC*H*HCHCH$_2$Ph), 2.59 (1H, dd, *J* 14.5, 8.5, CHCH$_2$SCH*H*CHCH$_2$Ph) and 1.20 (9H, s, C(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 177.8 (*C*O), 173.5 (*C*O), 135.5 (*i*-Ph), 129.1 (Ph), 129.0 (Ph), 127.5 (*p*-Ph), 58.0 (PhCH$_2$*C*HNH), 55.6 (^{t}BuCONH*C*H), 42.0 (CH*C*H$_2$Ph), 38.7 (*C*$(CH_3)_3$), 35.2 (S*C*H$_2$CHCH$_2$Ph), 30.8 (CH*C*H$_2$SCH$_2$CHCH$_2$Ph) and 27.4 (*C*H$_3$); *m*/*z* ($C_{17}H_{24}N_2NaOS$ ($M + Na^+$) requires 343.1451) found 343.1451. This compound has not previously been reported.

(*R*)-*tert*-Butyl-2-(benzyloxycarbonylamino)-3-(2-(*tert*-butoxycarbonyl(methyl) amino)ethylthio)propanoate (**2.124**)



Thiol coupling was carried out according to **General Method B** using 1-bromo-2-[*N*-(*tert*-butoxycarbonyl)-*N*-methylamino]ethane (2.4 g, 10 mmol) and **2.91** (3.1 g, 10 mmol). The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:9) to EtOAc) to give a colourless oil (1.3 g, 2.8 mmol, 28%); υ_{max} (cm^{-1}): 2979, 2930 ($COC(CH_3)_3$), 1699 (CO), 1513 (CH), 1376, 1341 ($C(CH_3)_3$), 1161 (CO); δ_H (400 MHz, $CDCl_3$) 7.39-7.28 (5H, m, Ph), 5.79 (1H, d, *J* 6.0, CH_2OCONH), 5.13 (2H, s, CH_2Ph), 4.61 (1H, dt, *J* 12.5, 6.0, CHNH), 3.46 (3H, s, NCH_3), 3.35 (2H, t, *J* 6.0, CH_2NCH_3), 3.12 (1H, dd, *J* 14.0, 5.5, CHCHHS), 2.92 (1H, dd, *J* 14.0, 5.5, CHCHHS), 2.69 (2H, t, *J* 6.0, SCH_2CH_2N), 1.42 (s, 9H, $C(CH_3)_3$) and 1.39 (s, 9H, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 171.0 ($CHCOO^tBu$), 155.9 (NHCO), 154.4 (NCO), 136.1 (*i*-Ph), 128.8 (Ph), 128.1 (*p*-Ph), 127.7 (Ph), 82.5 ($CHCOOC(CH_3)_3$), 79.9 ($NCOOC(CH_3)_3$, 66.9 (CH_2OCO), 57.9 (CONHCHCO), 56.0 (CH_2NCH_3), 35.5 (NCH_3), 34.1 ($CHCH_2S$), 30.6 (SCH_2CH_2N), 28.6 ($C(CH_3)_3$) and 28.2 ($C(CH_3)_3$); *m/z* ($C_{23}H_{36}N_2NaO_6S$ ($M + Na^+$) requires 491.2192) found 491.2191. This compound has not previously been reported.

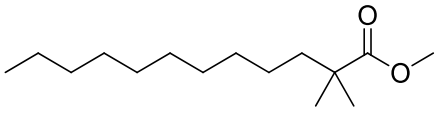
(*R*)-Methyl-6,6,13,13-tetramethyl-3,11-dioxo-1-phenyl-2,12-dioxa-7-thia-4,10-diazatetradecane-5-carboxylate (**2.130**)



Thiol coupling was carried out according to **General Method B** using (*R*)-methyl-2-(benzyloxycarbonylamino)-3-mercapto-3-methylbutanoate (0.3 g, 1 mmol) and **2.95** (0.2 g, 1 mmol). The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:1) to MeOH:EtOAc (1:9)) to give a colourless oil (0.1 g, 0.3 mmol, 31%); υ_{max} (cm^{-1}): 3330 (NH), 2992, 2935 ($COC(CH_3)_3$), 1698 (CO), 1511 (CH), 1398, 1346 ($C(CH_3)_3$), 1151 (CO); δ_H (400 MHz, $CDCl_3$) 7.43-7.31 (5H, m, Ph), 5.81 (1H, d, *J* 6.0, CH_2OCONH), 5.09 (2H, s, CH_2Ph), 4.99-5.06 (1H, s, CH_2NH), 4.48 (1H, d, *J* 6.0, CHNH), 3.71 (3H, s, OCH_3), 3.35-3.17 (2H, m, CH_2NH), 2.69 (2H, t, *J* 5.5, SCH_2CH_2NH), 1.55 (s, 6H, $C(CH_3)_2$) and 1.42 (s, 9H, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 171.1 ($CHCOOCH_3$), 155.9 (NHCO), 136.1 (*i*-Ph), 128.8 (Ph), 127.9 (*p*-Ph), 127.1 (Ph), 79.9 ($COOC(CH_3)_3$), 74.5 (CH(C)), 66.9 (CH_2OCO), 53.1 (OCH_3), 41.5 ($C(CH_3)_2$), 39.6 (CH_2NHCO), 30.3 ($C(CH_3)_2$), 28.4 (CH_3) and 27.0 (SCH_2); *m/z* ($C_{21}H_{32}N_2NaO_6S$ ($M + Na^+$) requires 463.1879) found 463.1883. This compound has not previously been reported.

General Method H: Lithium enolate alkylation

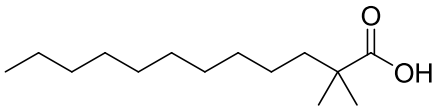
Methyl 2,2-dimethyl dodecanote (**2.136**)



Diisopropylamine (10.6 mL, 75 mmol) in THF (43.5 mL) with a small amount of phenanthroline indicator was cooled to -78 ^{o}C and 2.5 M ^{n}BuLi (25.0 mL, 62.5 mmol) was added dropwise and left stirring for 30 minutes, after which time methyl isobutyrate (8.6 ml, 75 mmol) was added and left stirring for a further 30 minutes. 1-Iododecane (12.3 mL, 57.7 mmol) was finally added to the solution and brought to room temperature overnight. The reaction mixture was concentrated *in vacuo* and the remaining mixture washed with *p*H 2 buffer and extracted with Petroleum Ether 40-60. The organics were collected and washed with sat. NaCl, dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude viscous liquid that was used without further purification; (14.5 g, 59.7 mmol, > 99%); δ_H (300 MHz, $CDCl_3$) 3.66-3.54 (3H, m, OC*H*$_3$), 1.52-1.37 (2H, m, C*H*$_2$C(CH$_3$)$_2$), 1.31-1.20 (10H, m, 5 × C*H*$_2$), 1.20 (6H, s, C(C*H*$_3$)$_2$), 1.12-1.10 (6H, m, 3 × CH_2) and 0.90-0.73 (3H, m, C*H*$_3$CH$_2$); *m*/*z* ($C_{15}H_{30}NaO_2$ (M + Na^+) requires 265.2138) found 265.2139. This compound is known but has previously been reported without any characterisation.[327-328]

General Method I: Ester hydrolysis

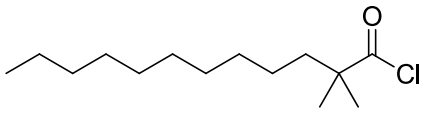
2,2-Dimethyl dodecanoic acid (**2.137**)



Crude ester **2.136** (14.5 g, 53.5 mmol) was refluxed overnight in EtOH (50 mL) and H_2O (3.5 mL) using KOH (6 g, 107 mmol). The mixture was cooled to room temperature and concentrated *in vacuo.* The mixture was then taken up in H_2O and extracted using a 1:1 mixture of Et_2O:Petroleum Ether 40-60 while maintaining the *p*H at ~8 using sodium phosphate buffer. The organics were combined, dried over sodium sulfate, filtered and concentrated *in vacuo* to give a clean colourless semi solid which required no further purification (8.3 g. 36.3

mmol, 63%); m.p.: 27-28 ^{o}C; υ_{max} (cm^{-1}) 2954, 2915, 2849 (CH_2, CO_2H), 1698 (CO_2H), 1464, 1454 (CH_2, CH_3), 1384 ($C(CH_3)_2$), 1326, 1309 (OH), 1290, 1272, 1245 (CO), 1189 (COH), 725 (CH_2); δ_H (400 MHz, $CDCl_3$) 10.40 (1H, br s, COO*H*), 1.60-1.50 (2H, m, C*H*$_2$C(CH$_3$)$_2$), 1.37-1.23 (16H, m, CH$_3$(C*H*$_2$)$_8$), 1.21 (6H, s, C(C*H*$_3$)$_2$) and 0.91 (3H, t, *J* 7.0, C*H*$_3$CH$_2$); δ_C (100 MHz, $CDCl_3$) 185.0 (*C*O), 42.2 (*C*(CH$_3$)$_2$), 40.6 (*C*H$_2$C(CH$_3$)$_2$), 31.9 (CH$_3$CH$_2$*C*H$_2$), 30.1, 29.65, 29.63, 29.5, 29.3 (CH$_3$CH$_2$CH$_2$*C*H$_2$*C*H$_2$*C*H$_2$*C*H$_2$*C*H$_2$), 24.9 (C(*C*H$_3$)$_2$), 24.8 (*C*H$_2$CH$_2$C(CH$_3$)$_2$), 22.6 (CH$_3$*C*H$_2$) and 14.1 (*C*H$_3$CH$_2$); *m*/*z* ($C_{14}H_{28}NaO_2$ (M + Na^+) requires 251.1982) found 251.1981. This compound is known but has previously only been reported with ^{1}H & ^{13}C NMR spectroscopic data.

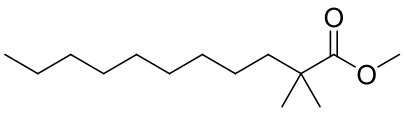
2,2-Dimethyldodecanoyl chloride (**2.138**)



2,2-Dimethyldodecanoyl chloride (**2.138**) was synthesised according to **General Method F** using **2.137** (0.2 g, 1 mmol) to give a colourless oil which was not isolated and used immediately without further purification (0.3 g, 1 mmol, > 99%). This compound is known but has previously been reported without any characterisation.[329]

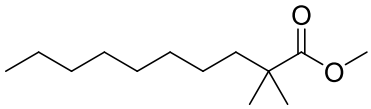
5.2.2 Long Chain Investigation Experimental

Methyl 2,2-dimethylundecanoate (**2.139**)



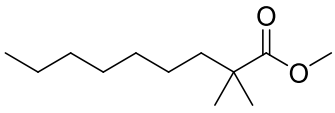
Lithium enolate alkylation was carried out according to **General Method H** using 1-iodononane (5.7 mL, 29 mmol) to give a crude viscous liquid that was used without further purification; (7.5 g, 33 mmol, > 99%); δ_H (300 MHz, $CDCl_3$) 3.68-3.58 (3H, m, OC*H*$_3$), 1.50-1.38 (2H, m, C*H*$_2$C(CH$_3$)$_2$), 1.28-1.12 (14H, m, CH$_3$(C*H*$_2$)$_7$CH$_2$), 1.13-1.05 (6H, 2 × s, C(C*H*$_3$)$_2$) and 0.89-0.75 (3H, m, C*H*$_3$CH$_2$); *m*/*z* ($C_{14}H_{29}O_2$ (M + H^+) requires 229.2162) found 229.2160. This compound has not previously been reported.

Methyl 2,2-dimethyldecanoate (**2.140**)



Lithium enolate alkylation was carried out according to **General Method H** using 1-iodooctane (5.2 mL, 29 mmol) to give a crude viscous liquid that was used without further purification; (7.0 g, 33 mmol, > 99%); δ_H (300 MHz, $CDCl_3$) 3.65-3.54 (3H, m, OC*H*$_3$), 1.48-1.36 (2H, m, C*H*$_2$C(CH$_3$)$_2$), 1.24-1.11 (12H, m, CH$_3$(C*H*$_2$)$_6$CH$_2$), 1.11-1.03 (6H, 2 × s, C(C*H*$_3$)$_2$) and 0.80 (3H, t, *J* 7.0, C*H*$_3$CH$_2$); *m*/*z* ($C_{13}H_{27}O_2$ (M + H^+) requires 215.2006) found 215.2001. This compound is known but has previously only been reported with IR data.[330-331]

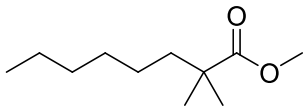
Methyl 2,2-dimethylnonanoate (**2.141**)



Lithium enolate alkylation was carried out according to **General Method H** using 1-iodoheptane (4.7 mL, 29 mmol) to give a crude viscous liquid that was used without further purification; (6.3 g, 31 mmol, > 99%); δ_H (300 MHz,

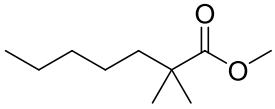
$CDCl_3$) 3.68-3.56 (3H, m, OC*H*$_3$), 1.50-1.39 (2H, m, C*H*$_2$C(CH_3)$_2$), 1.26-1.12 (10H, m, CH_3(C*H*$_2$)$_5$$CH_2$), 1.12-1.05 (6H, 2 × s, C(C*H*$_3$)$_2$) and 0.82 (3H, t, *J* 7.0, C*H*$_3$$CH_2$); *m*/*z* ($C_{12}H_{25}O_2$ (M + H^+) requires 201.1849) found 201.1848. This compound is known.[332]

Methyl 2,2-dimethyloctanoate (**2.142**)



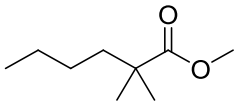
Lithium enolate alkylation was carried out according to **General Method H** using 1-iodohexane (4.3 mL, 29 mmol); (5.4 g, 29 mmol, >99 %); δ_H (300 MHz, $CDCl_3$) 3.66-3.52 (3H, m, OC*H*$_3$), 1.49-1.34 (2H, m, C*H*$_2$C(CH_3)$_2$), 1.24-1.11 (8H, m, CH_3(C*H*$_2$)$_4$$CH_2$), 1.11-1.02 (6H, 2 × s, C(C*H*$_3$)$_2$) and 0.78 (3H, t, *J* 7.0, C*H*$_3$$CH_2$); *m*/*z* ($C_{11}H_{23}O_2$ (M + H^+) requires 187.1693) found 187.1695. This data is consistent with that previously reported.[333]

Methyl 2,2-dimethylheptanoate (**2.143**)



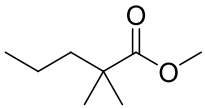
Lithium enolate alkylation was carried out according to **General Method H** using 1-iodopentane (3.8 mL, 29 mmol) to give a crude viscous liquid that was used without further purification; (5.0 g, 29 mmol, 99%); δ_H (400 MHz, $CDCl_3$) 3.54 (3H, s, OC*H*$_3$), 1.44-1.34 (2H, m, C*H*$_2$C(CH_3)$_2$), 1.21-1.06 (6H, m, CH_3(C*H*$_2$)$_3$), 1.05-1.03 (6H, 2 × s, C(C*H*$_3$)$_2$) and 0.80-0.74 (3H, m, C*H*$_3$$CH_2$); *m*/*z* ($C_{10}H_{21}O_2$ (M + H^+) requires 173.1536) found 173.1536. This data is consistent with that previously reported.[333]

Methyl 2,2-dimethylhexanoate (**2.144**)



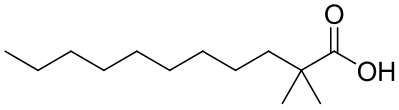
Lithium enolate alkylation was carried out according to **General Method H** using 1-iodobutane (2.8 mL, 29 mmol) to give a crude viscous liquid that was used without further purification; (2.9 g, 18 mmol, 63%); δ_H (400 MHz, $CDCl_3$) 3.54-3.46 (3H, m, OC*H*$_3$), 1.41-1.31 (2H, m, C*H*$_2$C(CH$_3$)$_2$), 1.13-1.02 (4H, m, CH$_3$(C*H*$_2$)$_2$), 1.03-0.97 (6H, 2 × s, C(C*H*$_3$)$_2$) and 0.77-0.68 (3H, m, C*H*$_3$CH$_2$); *m*/*z* ($C_9H_{19}O_2$ (M + H^+) requires 159.1380) found 159.1384. This data is consistent with that previously reported.[333]

Methyl 2,2-dimethylpentanoate (**2.145**)



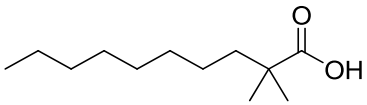
Lithium enolate alkylation was carried out according to **General Method H** using 1-iodopropane (2.4 mL, 25 mmol) to give a crude viscous liquid that was used without further purification; (2.8 g, 20 mmol, 78%); δ_H (400 MHz, $CDCl_3$) 3.62-3.50 (3H, m, OC*H*$_3$), 1.41-1.29 (2H, m, C*H*$_2$CCO), 1.28-1.21 (8H, m, CH$_3$C*H*$_2$CH$_2$C(C*H*$_3$)$_2$) and 0.76 (3H, t, *J* 7.0, C*H*$_3$CH$_2$); *m*/*z* ($C_8H_{17}O_2$ (M + H^+) requires 145.1223) found 145.1222. This data is consistent with that previously reported.[334]

2,2-Dimethylundecanoic acid (**2.146**)



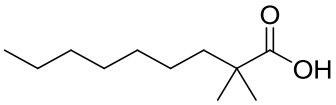
Ester hydrolysis was carried out according to **General Method I** using crude methyl 2,2-dimethylundecanote (**2.139**, 6.6 g, 29 mmol) to give a clean colourless oil (5.2 g, 24 mmol, 84%); υ_{max} (cm^{-1}) 2923, 2854 (CH_2, CH_3), 1698 (CO), 1466 (OH), 1408, 1365 ($C(CH_3)_2$), 1287, 1193 (CO); δ_H (400 MHz, $CDCl_3$) 11.15 (1H, br s, COO*H*), 1.58-1.47 (2H, m, C*H*$_2$C(CH$_3$)$_2$), 1.33-1.21 (14H, m, CH$_3$(C*H*$_2$)$_7$), 1.17 (6H, s, C(C*H*$_3$)$_2$) and 0.90-0.83 (3H, m, C*H*$_3$CH$_2$); δ_C (100 MHz, $CDCl_3$), 185.0 (*C*O), 42.1 (*C*(CH$_3$)$_2$), 40.5 (*C*H$_2$C(CH$_3$)$_2$), 35.6 (*C*H$_2$CH$_2$CH$_2$C(CH$_3$)$_2$), 30.1 (CH$_3$CH$_2$*C*H$_2$), 29.6, 29.5, 29.3 (CH$_3$CH$_2$CH$_2$*C*H$_2$*C*H$_2$*C*H$_2$), 24.9 (C(*C*H$_3$)$_2$), 24.8 (*C*H$_2$CH$_2$C(CH$_3$)$_2$), 22.7 (CH$_3$*C*H$_2$) and 14.0 (*C*H$_3$CH$_2$); *m*/*z* ($C_{13}H_{26}NaO_2$ (M + Na^+) requires 237.1825) found 237.1830. This compound is known but has previously been reported without any characterisation.[335]

2,2-Dimethyldecanoic acid (**2.147**)



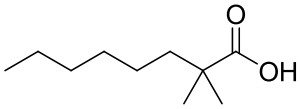
Ester hydrolysis was carried out according to **General Method I** using crude methyl 2,2-dimethyldecanote (**2.140**, 6.2 g, 29 mmol) to give a clean colourless oil (4.7 g, 23 mmol, 81%); υ_{max} (cm^{-1}) 2923, 2854 (CH_2, CH_3), 1698 (CO), 1474 (OH), 1407, 1365 ($C(CH_3)_2$), 1271, 1194 (CO); δ_H (400 MHz, $CDCl_3$) 10.71 (1H, br s, COO*H*), 1.57-1.45 (2H, m, C*H*$_2$C(CH$_3$)$_2$), 1.34-1.21 (12H, m, CH$_3$(C*H*$_2$)$_6$), 1.17 (6H, s, C(C*H*$_3$)$_2$) and 0.88 (3H, t, *J* 7.0, C*H*$_3$CH$_2$); δ_C (100 MHz, $CDCl_3$), 184.8 (*C*O), 42.2 (*C*(CH$_3$)$_2$), 40.6 (*C*H$_2$C(CH$_3$)$_2$), 31.9 (*C*H$_2$CH$_2$CH$_2$C(CH$_3$)$_2$), 30.2 (CH$_3$CH$_2$*C*H$_2$), 29.5, 29.3 (CH$_3$CH$_2$CH$_2$*C*H$_2$*C*H$_2$), 25.0 (C(*C*H$_3$)$_2$), 24.9 (*C*H$_2$CH$_2$C(CH$_3$)$_2$), 22.7 (CH$_3$*C*H$_2$) and 14.1 (*C*H$_3$CH$_2$); *m*/*z* ($C_{12}H_{24}NaO_2$ (M + Na^+) requires 223.1669) found 223.1672. This compound is known but has previously been reported without any NMR characterisation.[335]

2,2-Dimethylnonanoic acid (**2.148**)



Ester hydrolysis was carried out according to **General Method I** using crude methyl 2,2-dimethylnonanote (**2.141**, 5.8 g, 29 mmol) to give a clean colourless oil (3.7 g, 20 mmol, 69%); υ_{max} (cm^{-1}) 2923, 2855 (CH_2, CH_3), 1697 (CO), 1475 (OH), 1408, 1365 ($C(CH_3)_2$), 1282, 1247, 1198 (CO); δ_H (400 MHz, $CDCl_3$) 11.46 (1H, br s, COO*H*), 1.56-1.47 (2H, m, $CH_2C(CH_3)_2$), 1.35-1.21 (10H, m, $CH_3(CH_2)_5$), 1.18 (6H, s, $C(CH_3)_2$) and 0.86 (3H, t, *J* 7.0, CH_3CH_2); δ_C (100 MHz, $CDCl_3$), 185.2 (*C*O), 42.1 ($C(CH_3)_2$), 40.6 ($CH_2C(CH_3)_2$), 31.8 ($CH_2CH_2CH_2C(CH_3)_2$), 30.1 ($CH_3CH_2CH_2$), 29.2 ($CH_3CH_2CH_2CH_2$), 24.9 ($C(CH_3)_2$), 24.8 ($CH_2CH_2C(CH_3)_2$), 22.6 (CH_3CH_2) and 14.1 (CH_3CH_2); *m*/*z* ($C_{11}H_{22}NaO_2$ ($M + Na^+$) requires 209.1512) found 209.1518. This compound is known but has previously been reported with only ^{13}C NMR data.[336]

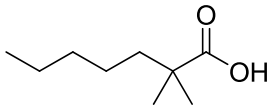
2,2-Dimethyloctanoic acid (**2.149**)



Ester hydrolysis was carried out according to **General Method I** using crude methyl 2,2-dimethyloctanote (**2.142**, 5.4 g, 29 mmol) to give a clean colourless oil (4.7 g, 27 mmol, 94%); υ_{max} (cm^{-1}) 2925, 2858 (CH_2, CH_3), 1697 (CO), 1475 (OH), 1409, 1366 ($C(CH_3)_2$), 1292, 1259, 1203 (CO); δ_H (400 MHz, $CDCl_3$) 11.52 (1H, br s, COO*H*), 1.57-1.48 (2H, m, $CH_2C(CH_3)_2$), 1.31-1.20 (8H, m, $CH_3(CH_2)_4$), 1.18 (6H, s, $C(CH_3)_2$) and 0.87 (3H, t, *J* 7.0, CH_3CH_2); δ_C (100 MHz, $CDCl_3$), 185.3 (*C*O), 42.2 ($C(CH_3)_2$), 40.6 ($CH_2C(CH_3)_2$), 31.7 ($CH_3CH_2CH_2$), 29.8 ($CH_3CH_2CH_2CH_2$), 24.9 ($C(CH_3)_2$), 24.8

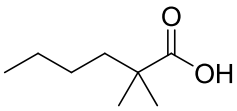
($CH_2CH_2C(CH_3)_2$), 22.6 (CH_3CH_2) and 14.1 (CH_3CH_2); *m*/*z* ($C_{10}H_{20}NaO_2$ (M + Na^+) requires 195.1356) found 195.1351. This data is consistent with that previously reported.[337]

2,2-Dimethylheptanoic acid (**2.150**)



Ester hydrolysis was carried out according to **General Method I** using crude methyl 2,2-dimethylheptanoate (**2.143**, 5.0 g, 29 mmol) to give a clean colourless oil (2.2 g, 14 mmol, 47%); υ_{max} (cm^{-1}) 2926, 2857 (CH_2, CH_3), 1697 (CO), 1475 (OH), 1409, 1366 ($C(CH_3)_2$), 1292, 1259, 1203 (CO); δ_H (400 MHz, $CDCl_3$) 10.81 (1H, br s, COO*H*), 1.56-1.45 (2H, m, $CH_2C(CH_3)_2$), 1.35-1.20 (6H, m, $CH_3(CH_2)_3$), 1.17 (6H, s, $C(CH_3)_2$) and 0.86 (3H, m, CH_3CH_2); δ_C (100 MHz, $CDCl_3$), 185.1 (*C*O), 42.1 ($C(CH_3)_2$), 40.5 ($CH_2C(CH_3)_2$), 32.3 ($CH_3CH_2CH_2$), 24.9 ($C(CH_3)_2$), 24.5 ($CH_2CH_2C(CH_3)_2$), 22.5 (CH_3CH_2) and 14.0 (CH_3CH_2); *m*/*z* ($C_9H_{18}NaO_2$ (M + Na^+) requires 181.1199) found 181.1207. This data is consistent with that previously reported.[338]

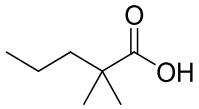
2,2-Dimethylhexanoic acid (**2.151**)



Ester hydrolysis was carried out according to **General Method I** using crude methyl 2,2-dimethylhexanote (**2.144**, 4.6 g, 29 mmol) to give a clean colourless oil (0.3 g, 2 mmol, 8%); υ_{max} (cm^{-1}) 2957, 2933, 2861 (CH_2, CH_3), 1698 (CO), 1475 (OH), 1408, 1366 ($C(CH_3)_2$), 1284, 1261, 1166 (CO); δ_H (400 MHz, $CDCl_3$) 9.89 (1H, br s, COO*H*), 1.52-1.46 (2H, m, $CH_2C(CH_3)_2$), 1.32-1.17 (4H,

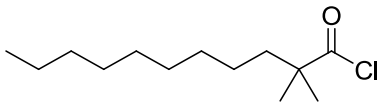
m, $CH_3(CH_2)_2$), 1.15 (6H, s, $C(CH_3)_2$) and 0.86 (3H, m, CH_3CH_2); δ_C (100 MHz, $CDCl_3$), 184.7 (*C*O), 42.1 ($C(CH_3)_2$), 40.3 ($CH_2C(CH_3)_2$), 27.1 ($CH_3CH_2CH_2$), 24.9 ($C(CH_3)_2$), 23.2 (CH_3CH_2) and 13.9 (CH_3CH_2); *m*/*z* ($C_8H_{16}NaO_2$ ($M + Na^+$) requires 167.1043) found 167.1043. This data is consistent with that previously reported.[336]

2,2-Dimethylhexanoic acid (**2.152**)



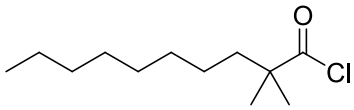
Ester hydrolysis was carried out according to **General Method I** using crude methyl 2,2-dimethylpentanote (**2.145**, 2.8 g, 19 mmol) to give a clean colourless oil (85 mg, 0.65 mmol, 3%); δ_H (400 MHz, $CDCl_3$) 9.44 (1H, br s, COO*H*), 1.56-1.46 (2H, m, $CH_2C(CH_3)_2$), 1.35-1.20 (2H, m, CH_3CH_2), 1.17 (6H, s, $C(CH_3)_2$) and 0.89 (3H, t, *J* 7.0, CH_3CH_2); δ_C (100 MHz, $CDCl_3$), 184.8 (*C*O), 42.0 ($C(CH_3)_2$), 41.1 ($CH_2C(CH_3)_2$), 24.9 ($C(CH_3)_2$), 18.2 (CH_3CH_2) and 14.0 (CH_3CH_2); *m*/*z* ($C_7H_{14}KO_2$ ($M + K^+$) requires 169.0625) found 169.0627. This data is consistent with that previously reported.[336]

2,2-Dimethylundecanoyl chloride (**2.154**)



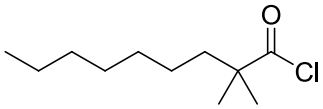
Acyl chloride was synthesised according to **General Method F** using 2,2-dimethylundecanoic acid (**2.146**, 0.2 g, 1 mmol) to give **2.154** (0.2 g, 1 mmol, 98%) a colourless oil which was not isolated and used immediately without further purification.

2,2-Dimethyldecanoyl chloride (**2.155**)



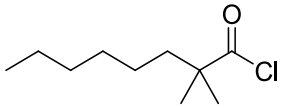
Acyl chloride was synthesised according to **General Method F** using 2,2-dimethyldecanoic acid (**2.147**, 0.2 g, 1 mmol) to give **2.155** (0.2 g, 1 mmol, 99%) a colourless oil which was not isolated and used immediately without further purification.

2,2-Dimethylnonanoyl chloride (**2.156**)



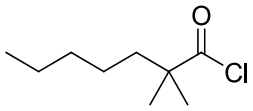
Acyl chloride was synthesised according to **General Method F** using 2,2-dimethylnonanoic acid (**2.148**, 0.2 g, 1 mmol) to give **2.156** (0.2 g, 1 mmol, 97%) a colourless oil which was not isolated and used immediately without further purification.

2,2-Dimethyloctanoyl chloride (**2.157**)



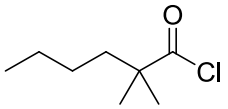
Acyl chloride was synthesised according to **General Method F** using 2,2-dimethyloctanoic acid (**2.149**, 0.2 g, 1 mmol) to give **2.157** (0.2 g, 1 mmol, 99%) a colourless oil which was not isolated and used immediately without further purification.

2,2-Dimethylheptanoyl chloride (**2.158**)



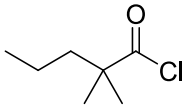
Acyl chloride was synthesised according to **General Method F** using 2,2-dimethylheptanoic acid (**2.150**, 0.2 g, 1 mmol) to give **2.158** (0.2 g, 1 mmol, 99%) a colourless oil which was not isolated and used immediately without further purification.

2,2-Dimethylhexanoyl chloride (**2.159**)



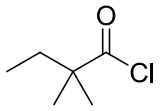
Acyl chloride was synthesised according to **General Method F** using 2,2-dimethylhexanoic acid (**2.151**, 0.1 g, 1 mmol) to give **2.159** (0.2 g, 1 mmol, 98%) a colourless oil which was not isolated and used immediately without further purification.

2,2-Dimethylpentanoyl chloride (**2.160**)



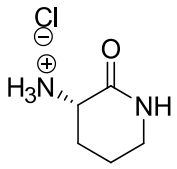
Acyl chloride was synthesised according to **General Method F** using 2,2-dimethylpentanoic acid (**2.152**, 85 mg, 0.65 mmol) to give **2.160** (97 mg, 0.65 mmol, 99%) a colourless oil which was not isolated and used immediately without further purification.

2,2-Dimethylbutanoyl chloride (**2.161**)



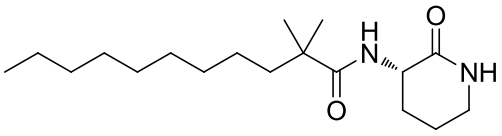
Acyl chloride was synthesised according to **General Method F** using commercially available 2,2-dimethylbutyric acid (**2.153**, 1.3 mL, 10 mmol) to give **2.161** (1.3 g, 9.6 mmol, 96%) a white solid which was not isolated and used immediately without further purification.

(*S*)-3-Aminopiperidin-2-one hydrochloride (**2.162**)



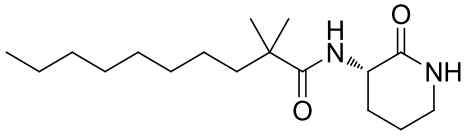
To a solution of (S)-3-benzyloxycarbonylaminopiperidin-2-one (5 g, 20 mmol, prepared according to the method described by Abe[339]) in MeOH (20.0 mL) was added Palladium on activated charcoal (0.2 g), and the suspension was stirred for 20 h at room temperature under a hydrogen atmosphere and filtered through a thin pad of celite©. After addition of 1 M HCl (20.0 mL, 20 mmol) to the filtrate, the mixture was evaporated under reduced pressure. The residue was crystallised by trituration in diethylether to give the product as a colourless powder (2.9 g, 19 mmol, 96%); $[\alpha]_D^{27}$ (c = 1, MeOH) -9.2; δ_H (400 MHz, D_2O) 3.97 (1H, dd, *J* 11.5, 6.5, C*H*CONH), 3.40 (2H, td, *J* 4.0, 6.0, CH_2NH), 2.32 (1H, m, CHC*H*H), 2.01 (1H, m, CHCH_2C*H*H), 1.81–1.97 (2H, m, CHCH*H*CH*H*); δ_C (100 MHz, D_2O) 171.6 (*C*O), 52.3 (*C*H), 44.0 (*C*H_2NH), 27.6 (CH*C*H_2), 22.7 (CHCH_2*C*H_2); *m*/*z* ($C_5H_{11}N_2O$ ([M + H]$^+$) requires 115.0866) found 115.0867. This data is consistent with that previously reported.[340]

(*S*)-3-(Dimethylundecanoylamino)tetrahydropyridin-2-one (**2.163**)



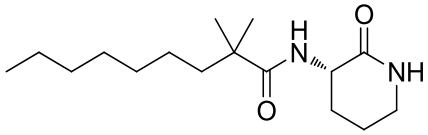
Acylation was carried out according to **General Method E** using **2.162** (0.2 g, 1 mmol), **2.154** (0.2 g, 1 mmol) and 2 mL of H_2O and dichloromethane. The residue was purified by hydrogenation and silica column chromatography (eluent; EtOAc:Petroleum Ether 40-60 (2:8) to EtOAc:Petroleum Ether 40-60 (1:1)) to give a clear viscous liquid (50 mg, 0.16 mmol, 16%); υ_{max} (cm^{-1}) 3321 (CONH), 2922, 2853 (CH_2, CH_3), 1637 (CONH lactam), 1523, 1491 (NH), 1360 ($C(CH_3)_2$) and 1331 (CH_3); δ_H (400 MHz, $CDCl_3$) 6.65 (1H, d, *J* 5.0, N*H*CH), 6.59 (1H, br s, N*H*CH_2), 4.16 (1H, dt, *J* 11.5, 5.5, NHC*H*), 3.30 (2H, td, *J* 6.5, 2.5 NHC*H*$_2$), 2.53 (1H, tdd, *J* 13.0, 6.0, 4.5, CHC*H*H), 1.92-1.82 (2H, m, $CHCH_2CH_2$), 1.54-1.37 (3H, m, $CH_2C(CH_3)_2$ & CHC*H*H), 1.30-1.16 (14H, m, $CH_3(CH_2)_7$), 1.14 (3H, s, $CH_2C(CH_3)_2$), 1.13 (3H, s, $CH_2C(CH_3)_2$) and 0.84 (3H, t, *J* 7.0, CH_3CH_2); δ_C (100 MHz, $CDCl_3$) 178.1 (*C*ONHCH), 172.2 (*C*ONHCH$_2$), 50.5 (CONH*C*H), 42.0 ($C(CH_3)_2$), 41.4, 41.3 ($CH_2C(CH_3)_2$ & NHCH_2), 31.8, 30.8 ($CH_3CH_2CH_2CH_2CH_2CH_2CH_2$), 29.50, 29.47, 29.2 ($CH_3CH_2CH_2CH_2CH_2CH_2$), 26.9 ($CHCH_2$), 25.25 ($C(CH_3)_2$), 25.20 ($C(CH_3)_2$), 24.7 ($CH_2CH_2C(CH_3)_2$), 22.6 ($CH_3CH_2$), 20.9 ($CHCH_2CH_2$) and 14.0 ($CH_3CH_2$); *m*/*z* ($C_{18}H_{35}N_2O_2$ ($M + H^+$) requires 311.2693) found 311.2692. This compound has not previously been reported.

(*S*)-3-(Dimethyldecanoylamino)tetrahydropyridin-2-one (**2.164**)



Acylation was carried out according to **General Method E** using **2.162** (0.2 g, 1 mmol), **2.155** (0.2 g, 1 mmol) and 2 mL of H_2O and dichloromethane. The residue was purified by hydrogenation and silica column chromatography (eluent; EtOAc to EtOAc:MeOH (9:1)) to give a clear viscous liquid (91 mg, 0.31 mmol, 31%); υ_{max} (cm^{-1}) 3302 (CONH), 2923, 2854 (CH_2, CH_3), 1637 (CONH lactam), 1524, 1491 (NH), 1360 ($C(CH_3)_2$) and 1330 (CH_3); δ_H (400 MHz, $CDCl_3$) 6.82 (1H, br s, N*H*CH_2), 6.65 (1H, d, *J* 5.0, N*H*CH), 4.13 (1H, dt, *J* 11.5, 5.5, NHC*H*), 3.33-3.21 (2H, m, NHC*H*$_2$), 2.55-2.43 (1H, m, CHC*H*H), 1.90-1.78 (2H, m, $CHCH_2CH_2$), 1.55-1.35 (3H, m, C*H*$_2$C$(CH_3)_2$ & CHC*H*H), 1.26-1.14 (12H, m, $CH_3(CH_2)_6$), 1.12 (3H, s, $CH_2C(CH_3)_2$), 1.11 (3H, s, $CH_2C(CH_3)_2$) and 0.81 (3H, t, *J* 6.5, CH_3CH_2); δ_C (100 MHz, $CDCl_3$) 178.0 (*C*ONHCH), 172.2 (*C*ONHCH_2), 50.4 (CONH*C*H), 42.0 (*C*$(CH_3)_2$), 41.34, 41.26 ($CH_2C(CH_3)_2$ & NH*C*H_2), 31.7, 30.8 ($CH_3CH_2CH_2CH_2CH_2CH_2$), 29.4, 29.1 ($CH_3CH_2CH_2CH_2CH_2$), 26.8 (CH*C*H_2), 25.2 (C(*C*$H_3)_2$), 25.1 (C(*C*$H_3)_2$), 24.6 ($CH_2CH_2C(CH_3)_2$), 22.5 (CH_3CH_2), 20.9 ($CHCH_2CH_2$) and 14.0 (CH_3CH_2); *m*/*z* ($C_{17}H_{33}N_2O_2$ ($M + H^+$) requires 297.2537) found 297.2532. This compound has not previously been reported.

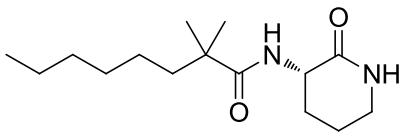
(*S*)-3-(Dimethylnonanoylamino)tetrahydropyridin-2-one (**2.165**)



Acylation was carried out according to **General Method E** using **2.162** (0.2 g, 1 mmol), **2.156** (0.2 g, 1 mmol) and 2 mL of H_2O and dichloromethane. The residue was purified by hydrogenation and silica column chromatography (eluent; EtOAc to EtOAc:MeOH (9:1)) to give a clear viscous liquid (47 mg, 0.16 mmol, 17%); υ_{max} (cm^{-1}) 3302 (CONH), 2924 (CH_2, CH_3), 1637 (CONH lactam), 1525, 1491 (NH), 1361 ($C(CH_3)_2$) and 1331 (CH_3); δ_H (400 MHz,

$CDCl_3$) 6.64 (1H, d, *J* 5.0, N*H*CH), 6.48 (1H, br s, N*H*CH_2), 4.17 (1H, dt, *J* 11.5, 5.5, NHC*H*), 3.31 (2H, td, *J* 6.5, 2.5 NHC*H*$_2$), 2.55 (1H, tdd, *J* 13.0, 6.0, 4.5, CHC*H*H), 1.94-1.84 (2H, m, $CHCH_2CH_2$), 1.55-1.41 (3H, m, $CH_2C(CH_3)_2$ & CHC*H*H), 1.31-1.18 (10H, m, $CH_3(CH_2)_5$), 1.15 (3H, s, $CH_2C(CH_3)_2$), 1.14 (3H, s, $CH_2C(CH_3)_2$) and 0.84 (3H, t, *J* 7.0, CH_3CH_2); δ_C (100 MHz, $CDCl_3$) 178.2 (*C*ONHCH), 172.2 (*C*O$NHCH_2$), 50.5 (CONH*C*H), 42.1 ($C(CH_3)_2$), 41.5, 41.3 ($CH_2C(CH_3)_2$ & $NHCH_2$), 31.8, 30.1 ($CH_3CH_2CH_2CH_2CH_2$), 29.1 ($CH_3CH_2CH_2CH_2$), 26.9 ($CHCH_2$), 25.26 ($C(CH_3)_2$), 25.22 ($C(CH_3)_2$), 24.7 ($CH_2CH_2C(CH_3)_2$), 22.6 (CH_3CH_2), 20.9 ($CHCH_2CH_2$) and 14.0 (CH_3CH_2); *m*/*z* ($C_{16}H_{30}N_2NaO_2$ ($M + Na^+$) requires 305.2199) found 305.2196. This compound has not previously been reported.

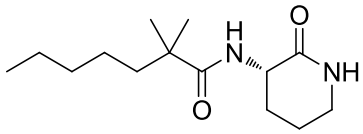
(*S*)-3-(Dimethyloctanoylamino)tetrahydropyridin-2-one (**2.166**)



Acylation was carried out according to **General Method E** using **2.162** (0.2 g, 1 mmol), **2.157** (0.2 g, 1 mmol) and 2 mL of H_2O and dichloromethane. The residue was purified by hydrogenation and silica column chromatography (eluent; EtOAc to EtOAc:MeOH (9:1)) to give a clear viscous liquid (37 mg, 0.14 mmol, 14%); υ_{max} (cm^{-1}) 3311 (CONH), 2927 (CH_2, CH_3), 1636 (CONH lactam), 1525, 1491 (NH), 1360 ($C(CH_3)_2$) and 1331 (CH_3); δ_H (400 MHz, $CDCl_3$) 6.63 (1H, d, *J* 5.0, N*H*CH), 6.47 (1H, br s, N*H*CH_2), 4.17 (1H, dt, *J* 11.5, 5.5, NHC*H*), 3.31 (2H, td, *J* 6.5, 2.5 NHC*H*$_2$), 2.55 (1H, tdd, *J* 13.0, 6.0, 4.5, CHC*H*H), 1.94-1.84 (2H, m, $CHCH_2CH_2$), 1.55-1.40 (3H, m, $CH_2C(CH_3)_2$ & CHC*H*H), 1.29-1.18 (8H, m, $CH_3(CH_2)_4$), 1.15 (3H, s, $CH_2C(CH_3)_2$), 1.14 (3H, s, $CH_2C(CH_3)_2$) and 0.84 (3H, t, *J* 6.5, CH_3CH_2); δ_C (100 MHz, $CDCl_3$) 178.2 (*C*ONHCH), 172.2 (*C*O$NHCH_2$), 50.5 (CONH*C*H), 42.1 ($C(CH_3)_2$), 41.5, 41.3

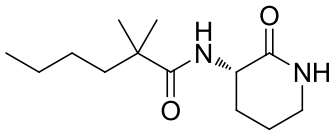
(*C*H_2C(CH_3)$_2$ & NH*C*H_2), 31.7 (CH_3CH_2*C*H_2), 29.7 ($CH_3CH_2CH_2$*C*H_2), 26.9 (CH*C*H_2), 25.26 (C(*C*H_3)$_2$), 25.21 (C(*C*H_3)$_2$), 24.6 (*C*H_2CH_2C(CH_3)$_2$), 22.5 (CH_3*C*H_2), 20.9 ($CHCH_2$*C*H_2) and 14.0 (*C*H_3CH_2); *m*/*z* ($C_{15}H_{28}N_2NaO_2$ (M + Na^+) requires 291.2043) found 291.2043. This compound has not previously been reported.

(*S*)-3-(Dimethylheptanoylamino)tetrahydropyridin-2-one (**2.167**)



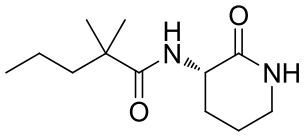
Acylation was carried out according to **General Method E** using **2.162** (0.2 g, 1 mmol), **2.158** (0.2 g, 1 mmol) and 2 mL of H_2O and dichloromethane. The residue was purified by hydrogenation and silica column chromatography (eluent; EtOAc to EtOAc:MeOH (9:1)) to give a clear viscous liquid (105 mg, 0.41 mmol, 41%); υ_{max} (cm^{-1}) 3321 (CONH), 2930 (CH_2, CH_3), 1636 (CONH lactam), 1524, 1491 (NH), 1360 (C(CH_3)$_2$) and 1330 (CH_3); δ_H (400 MHz, $CDCl_3$) 6.87 (1H, br s, N*H*CH_2), 6.66 (1H, d, *J* 5.0, N*H*CH), 4.12 (1H, dt, *J* 11.5, 5.5, NHC*H*), 3.31-3.21 (2H, m, NHC*H*$_2$), 2.52-2.41 (1H, m, CHC*H*H), 1.89-1.78 (2H, m, $CHCH_2$C*H*$_2$), 1.53-1.36 (3H, m, C*H*$_2$C(CH_3)$_2$ & CHC*H*H), 1.28-1.13 (6H, m, CH_3(C*H*$_2$)$_3$), 1.11 (3H, s, CH_2C(C*H*$_3$)$_2$), 1.10 (3H, s, CH_2C(C*H*$_3$)$_2$) and 0.79 (3H, t, *J* 7.0, C*H*$_3CH_2$); δ_C (100 MHz, $CDCl_3$) 178.0 (*C*ONHCH), 172.2 (*C*O$NHCH_2$), 50.3 (CONH*C*H), 41.9 (*C*(CH_3)$_2$), 41.3, 41.2 (*C*H_2C(CH_3)$_2$ & NH*C*H_2), 32.2 (CH_3CH_2*C*H_2), 26.8 (CH*C*H_2), 25.18 (C(*C*H_3)$_2$), 25.11 (C(*C*H_3)$_2$), 24.2 (*C*H_2CH_2C(CH_3)$_2$), 22.4 (CH_3*C*H_2), 20.9 ($CHCH_2$*C*H_2) and 13.9 (*C*H_3CH_2); *m*/*z* ($C_{14}H_{26}N_2NaO_2$ (M + Na^+) requires 277.1886) found 277.1888. This compound has not previously been reported.

(*S*)-3-(Dimethylhexanoylamino)tetrahydropyridin-2-one (**2.168**)



Acylation was carried out according to **General Method E** using **2.162** (0.2 g, 1 mmol), **2.159** (0.2 g, 1 mmol) and 2 mL of H_2O and dichloromethane. The residue was purified by hydrogenation and silica column chromatography (eluent; EtOAc to EtOAc:MeOH (9:1)) to give a clear viscous liquid (83 mg, 0.34 mmol, 34%); υ_{max} (cm^{-1}) 3305 (CONH), 2930, 2860 (CH_2, CH_3), 1636 (CONH lactam), 1524, 1491 (NH), 1359 ($C(CH_3)_2$) and 1330 (CH_3); δ_H (400 MHz, $CDCl_3$) 6.72 (1H, br s, N*H*CH_2), 6.65 (1H, d, *J* 5.0, N*H*CH), 4.19-4.10 (1H, m, NHC*H*), 3.32-3.25 (2H, m, NHC*H*$_2$), 2.56-2.46 (1H, m, CHC*H*H), 1.91-1.81 (2H, m, $CHCH_2CH_2$), 1.54-1.38 (3H, m, $CH_2C(CH_3)_2$ & CHC*H*H), 1.30-1.14 (4H, m, $CH_3CH_2CH_2$), 1.13 (3H, s, $CH_2C(CH_3)_2$), 1.12 (3H, s, $CH_2C(CH_3)_2$) and 0.85-0.80 (3H, m, CH_3CH_2); δ_C (100 MHz, $CDCl_3$) 178.1 (*C*ONHCH), 172.2 (*C*O$NHCH_2$), 50.4 (CONH*C*H), 42.0 ($C(CH_3)_2$), 41.4, 41.0 ($CH_2C(CH_3)_2$ & $NHCH_2$), 26.9 ($CH_3CH_2CH_2$), 26.8 ($CHCH_2$), 25.23 ($C(CH_3)_2$), 25.16 ($C(CH_3)_2$), 23.1 (CH_3CH_2), 20.9 ($CHCH_2CH_2$) and 13.9 (CH_3CH_2); *m*/*z* ($C_{13}H_{24}N_2NaO_2$ (M + Na^+) requires 263.1730) found 263.1731. This compound has not previously been reported.

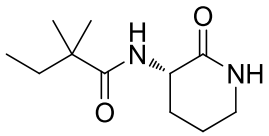
(*S*)-3-(Dimethylpentanoylamino)tetrahydropyridin-2-one (**2.169**)



Acylation was carried out according to **General Method E** using **2.162** (100 mg, 0.65 mmol), **2.160** (97 mg, 0.65 mmol) and 2 mL of H_2O and dichloromethane. The residue was purified by silica column chromatography (eluent; EtOAc to

EtOAc:MeOH (9:1)) to give a white crystalline solid (10 mg, 0.04 mmol, 7%); m.p.: 105-106 ^{o}C; υ_{max} (cm^{-1}) 3342 (CONH), 2960, 2905 (CH_2, CH_3), 1641 (CONH lactam), 1580, 1499 (NH), 1333 ($C(CH_3)_2$); δ_H (400 MHz, $CDCl_3$) 6.60 (1H, d, *J* 5.0, N*H*CH), 5.82 (1H, br s, N*H*CH_2), 4.21 (1H, dt, *J* 11.5, 5.5, NHC*H*), 3.37-3.32 (2H, m, NHC*H*$_2$), 2.66-2.57 (1H, m, CHC*H*H), 1.99-1.88 (2H, m, $CHCH_2CH_2$), 1.56-1.43 (3H, m, $CH_2C(CH_3)_2$ & CHC*H*H), 1.34-1.20 (2H, m, CH_3CH_2), 1.18 (3H, s, $CH_2C(CH_3)_2$), 1.17 (3H, s, $CH_2C(CH_3)_2$) and 0.89 (3H, t, *J* 7.0, CH_3CH_2); δ_C (100 MHz, $CDCl_3$) 178.1 (*C*ONHCH), 172.2 (*C*ONHCH$_2$), 50.7 (CONH*C*H), 42.4 ($C(CH_3)_2$), 41.7, 41.5 ($CH_2C(CH_3)_2$ & NHCH_2), 26.9 ($CHCH_2$), 25.3 ($C(CH_3)_2$), 25.2 ($C(CH_3)_2$), 20.8 ($CHCH_2CH_2$), 17.2 (CH_3CH_2) and 14.0 (CH_3CH_2); *m*/*z* ($C_{12}H_{22}N_2NaO_2$ (M + Na$^+$) requires 249.1579) found 249.1581. This compound has not previously been reported.

(*S*)-3-(Dimethylbutanoylamino)tetrahydropyridin-2-one (**2.170**)

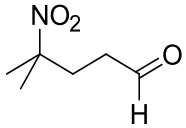


Acylation was carried out according to **General Method E** using **2.162** (1.5 g, 1 mmol), **2.160** (1.3 g, 1 mmol) and 10 mL of H_2O and dichloromethane. The residue was purified by silica column chromatography (eluent; EtOAc to EtOAc:MeOH (9:1)) to give a viscous liquid with impurities. The compound was purified further by silica column chromatography (eluent; EtOAc:MeOH (99:1)) to give a white solid (12 mg, 0.06 mmol, 0.6%); m.p.: 108-109 ^{o}C; υ_{max} (cm^{-1}) 3372 (CONH), 2901, 2899 (CH_2, CH_3), 1639 (CONH lactam), 1564, 1484 (NH), 1302 ($C(CH_3)_2$); δ_H (400 MHz, $CDCl_3$) 6.78 (1H, br s, N*H*CH_2), 6.65 (1H, d, *J* 5.0, N*H*CH), 4.14 (1H, dt, *J* 11.5, 5.5, NHC*H*), 3.27 (2H, td, *J* 6.5, 2.5 NHC*H*$_2$), 2.49 (1H, tdd, *J* 13.0, 6.0, 4.5, CHC*H*H), 1.89-1.80 (2H, m, $CHCH_2CH_2$), 1.56-1.41 (3H, m, CH_3CH_2 & CHC*H*H), 1.11 (3H, s, $CH_2C(CH_3)_2$), 1.10 (3H, s,

$CH_2C(CH_3)_2$) and 0.78 (3H, t, *J* 7.5, CH_3CH_2); δ_C (100 MHz, $CDCl_3$) 177.9 (*C*ONHCH), 172.1 (*C*ONHCH$_2$), 50.3 (CONH*C*H), 42.3 (*C*(CH$_3$)$_2$), 41.3 (NH*C*H$_2$), 33.8 (CH$_3$*C*H$_2$), 26.9 (CH*C*H$_2$), 24.8 (C(*C*H$_3$)$_2$), 24.6 (C(*C*H$_3$)$_2$), 20.9 (CHCH$_2$*C*H$_2$) and 9.0 (*C*H$_3$CH$_2$); *m*/*z* ($C_{11}H_{20}N_2NaO_2$ (M + Na^+) requires 235.1417) found 235.1418. This compound has not previously been reported.

5.3 Chapter 3 Experimental

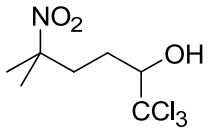
4-Methyl-4-nitropentanal (**3.51**)



To a solution of 2-nitropropane (**3.49**, 20.0 mL, 0.22 mol) in acetonitrile (100 mL) at 0 ^oC was added freshly distilled acrolein (**3.50**, 24.0 mL, 0.36 mol) followed by the dropwise addition of triethylamine (2.0 mL). The reaction was stirred at room temperature for three days. The mixture was concentrated *in vacuo* to give a crude viscous yellow oil which was used without further purification (32 g, > 99%); υ_{max} (cm^{-1}) 2922, 2851 (CH_2, CH_3), 2831, 2720 (CHO), 1728 (CO), 1523 (CNO_2), 1360 ($C(CH_3)_2$) and 1349 (NO_2); δ_H (400 MHz, $CDCl_3$) 9.78 (1H, s, C*H*O), 2.51 (2H, t, *J* 8.0, C*H*$_2$CHO), 2.24 (2H, t, *J* 8.0, C*H*$_2$CH$_2$CHO) and 1.60 (6H, s, C(C*H*$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 199.9 (*C*HO), 86.9 (*C*NO$_2$), 38.1 (CH$_2$*C*HO), 31.7 (*C*H$_2$CH$_2$CHO) and 25.1 (C(*C*H$_3$)$_2$); *m*/*z* ($C_6H_{12}NO_3$ (M + H^+) requires 146.0812) found 146.0814. This data is consistent with that previously reported.[274]

General Method J: Trichlorocarbinol synthesis from its aldehyde

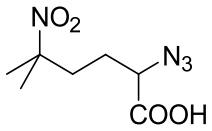
1,1,1-Trichloro-5-methyl-5-nitrohexan-2-ol (**3.52**)



To a stirred solution of **3.51** (35.0 g, 0.24 mol) and trichloroacetic acid (59.0 g, 0.36 mol) in DMF (240 mL) at 0 ^{o}C was added sodium trichloroacetate (67.0 g, 0.36 mol) portion wise with stirring. The reaction mixture was brought to room temperature and left stirring overnight during which time the reaction mixture slightly solidified and a distinct colour change from orange to dark brown was observed. After 18 h ^{1}H-NMR showed complete consumption of **3.51**. The reaction mixture was cooled to 0 ^{o}C and quenched with H_2O and extracted with EtOAc:Hexane (4:6). The combined organic extracts were washed with H_2O:*sat.* NH_4Cl (1:1), dried over sodium sulfate, filtered and concentrated *in vacuo* to give a viscous brown oil. The residue was purified by silica column chromatography (eluent; Petroleum Ether 40-60:EtOAc (9:1) to EtOAc) to give a light yellow oil (48.0 g, 0.18 mol, 76%); υ_{max} (cm^{-1}) 3279 (OH), 3067, 2993, 2943 (CH_2, CH_3), 1554, 1536 (CNO_2), 1485 (NO_2), 1371 ($C(CH_3)_2$), 1353 (CNO_2), 1254, 1136, 1102 (CO), 719 (CH_2); δ_H (400 MHz, $CDCl_3$) 3.97 (1H, ddd, *J* 10.0, 5.0, 1.5, C*H*OH), 3.30 (1H, br s, O*H*), 2.27 (1H, ddd, *J* 13.5, 12.0, 5.0, C*H*HCH$_2$CH), 2.12-1.95 (2H, m, C*H*HCHOH & C*H*HCH$_2$CH), 1.68-1.63 (1H, m, CH*H*CHOH), 1.62 (3H, s, C(C*H*$_3$)$_2$) and 1.61 (3H, s, C(C*H*$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 103.5 (*C*Cl_3), 87.7 (*C*NO_2), 82.6 (*C*H), 37.1 (*C*H$_2$CH$_2$CH), 26.5 (C(*C*H$_3$)$_2$), 26.4 (*C*H$_2$CHOH) and 25.3 (C(*C*H$_3$)$_2$); *m*/*z* ($C_7H_{11}NNaO_3$ ([M – HCl_3 + Na]$^{+}$) requires 180.0631) found 180.0636. This compound has not previously been reported.

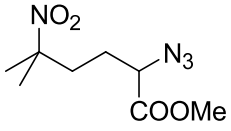
General Method K: α-Azido acid synthesis from its trichlorocarbinol

2-Azido-5-methyl-5-nitrohexanoic acid (**3.53**)



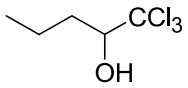
Trichlorocarbinol **3.52** (0.6 g, 2.3 mmol) was dissolved in 1,2-dimethoxyethane (4 mL) and cooled to 0 ^{o}C. Sodium azide (0.3 g, 4.6 mmol) was carefully added to a cooled solution of sodium hydroxide (0.36 g, 9 mmol) in H_2O (18 mL). Both cold solutions were combined slowly behind a blast shield and after 1 hr was brought to room temperature and left stirring vigorously until the reaction was deemed complete by TLC analysis (18 h). The solution was quenched with diethyl ether and extracted with 5% aq. NaOH solution. The aqueous layers were combined, acidified to *p*H 2 with 1M HCl, extracted with ethyl acetate, and the combined organic layers dried over sodium sulfate, filtered and concentrated *in vacuo* to give an orange crystalline product (0.5 g, 2.1 mol, 92%); υ_{max} (cm^{-1}) 3064, 2940 (CH_2, CH_3), 2871 (OH), 2144 (N_3), 1723 (COOH), 1558, 1536 (CNO_2), 1487 (NO_2), 1368 ($C(CH_3)_2$), 1352 (CNO_2), 1249, 1135 (CO), 718 (CH_2); δ_H (400 MHz, $CDCl_3$) 8.58 (1H, br s, COO*H*), 3.99 (1H, dd, *J* 8.0, 5.0, C*H*N_3), 2.05 (2H, t, *J* 8.5, C*H*$_2$$CH_2CHN_3$), 1.92-1.69 (2H, m, C*H*$_2$$CHN_3$), 1.61 (3H, s, $C(CH_3)_2$) and 1.60 (3H, s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 174.7 (*C*OOH), 87.4 (*C*NO_2), 61.2 (*C*HN_3), 36.4 (*C*H_2CHN_3), 26.1 (*C*H_2CH_2CH), 26.0 ($C(CH_3)_2$) and 25.6 ($C(CH_3)_2$); *m*/*z* ($C_7H_{12}N_4NaO_4$ ($M + Na^+$) requires 239.0751) found 239.0753. This compound has not previously been reported.

Methyl 2-azido-5-methyl-5-nitrohexanoate (**3.59**)



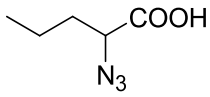
Acetyl chloride (0.1 mL, 1.1 mmol) was added dropwise to an ice cold solution of **3.53** (0.2 g, 1 mmol) in ethyl acetate (5 mL) and MeOH (0.2 mL) under nitrogen. After 2 h the reaction mixture was allowed to warm to room temperature and the mixture concentrated *in vacuo* to give an orange crystalline product (0.2 g, 0.8 mmol, 82%); υ_{max} (cm^{-1}) 3062, 2938 (CH_2, CH_3), 2144 (N_3), 1715 (CO), 1559, 1540 (CNO_2), 1472 (NO_2), 1368 ($C(CH_3)_2$), 1351 (CNO_2), 1239, 1134 (CO), 718 (CH_2); δ_H (400 MHz, $CDCl_3$) 3.95 (1H, dd, *J* 8.0, 5.0, C*H*N_3), 3.66 (3H, s, COOC*H*$_3$), 2.11 (2H, t, *J* 9.0, C*H*$_2$$CH_2CHN_3$), 1.89-1.67 (2H, m, C*H*$_2$$CHN_3$), 1.68 (3H, s, C(C*H*$_3$)$_2$) and 1.61 (3H, s, C(C*H*$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 171.0 (*C*OOH), 87.5 (*C*NO_2), 63.5 (*C*HN_3), 51.5 (O*C*H_3), 34.6 (*C*H_2CHN_3), 26.8 (*C*H_2CH_2CH), 25.8 (C(*C*H_3)$_2$) and 25.1 (C(*C*H_3)$_2$); *m*/*z* ($C_8H_{14}N_4NaO_4$ ($M + Na^+$) requires 253.0913) found 253.0916. This compound has not previously been reported.

1,1,1-trichloropentan-2-ol (**3.62**)



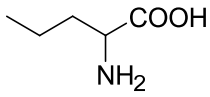
Trichloroalconation was carried out according to **General Method J** using butyraldehyde (1.0 g, 14 mmol) to give a viscous orange oil. The residue was purified by silica column chromatography (eluent; Petroleum Ether 40-60:EtOAc (1:1) to EtOAc) to give a colourless oil (2.0 g, 10 mol, 72%); υ_{max} (cm^{-1}) 3595 (OH), 3058, 2951, 1423, 1390 (CH_2, CH_3); δ_H (400 MHz, $CDCl_3$) 3.95 (1H, dd, *J* 9.5, 2.0 C*H*OH), 3.67 (1H, br s, O*H*), 1.95-1.86 (1H, m, C*H*HCH), 1.67-1.52 (2H, m, C*H*HC*H*HCH), 1.45-1.36 (1H, m, C*H*HCH_2CH) and 0.93 (3H, t, *J* 7.5, C*H*$_3$$CH_2$); δ_C (100 MHz, $CDCl_3$) 104.4 (*C*Cl_3), 82.5 (*C*HOH), 33.5 (*C*H_2CH), 19.2 (*C*H_2CH_2CH) and 13.6 (*C*H_3). This data is consistent with that previously reported.[341]

2-Azidopentanoic acid (**3.63**)



The α-azido acid **3.63** was generated by **General Method K** using **3.62** (1.9 g, 10 mmol) to give a viscous oil which was used without further purification (1.1 g, 7.6 mol, 77%); υ_{max} (cm^{-1}) 2953, 2928, (CH_2, CH_3) 2870 (COOH), 2144 (N_3), 1712 (CO), 1571 (COO), 1414, 1376 (CH_2, CH_3); δ_H (400 MHz, $CDCl_3$) 10.10 (1H, br s, COO*H*), 3.87 (1H, dd, *J* 8.5, 5.5, C*H*N_3), 1.91-1.71 (2H, m, C*H*$_2$CHN_3), 1.57-1.38 (2H, m, CH_3C*H*$_2$) and 0.96 (3H, t, *J* 7.5 C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 176.3 (*C*OOH), 61.5 (*C*HN_3), 33.2 (*C*H_2CHN_3), 19.0 (CH_3*C*H_2) and 13.4 (*C*H_3); *m*/*z* 143.1 ($M + Na^+$). This data is consistent with that previously reported.[342]

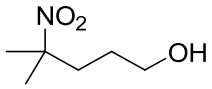
2-Aminopentanoic acid (**3.64**)



To a solution of **3.63** (0.43 g, 3 mmol) in the minimum amount of MeOH was added Palladium on carbon (5 mol %) and stirred at room temperature under an atmosphere of hydrogen. After the reaction was deemed complete, by TLC analysis, the mixture was filtered through a thin pad of celite©, and washed successively with MeOH. The extracts were concentrated *in vacuo* to give a white crystalline product (0.26 g, 2.2 mol, 74%); m.p.: > 250 ^oC; υ_{max} (cm^{-1}) 3248 (NH_2), 2955, 2931, (CH_2, CH_3) 2871 (COOH), 1719 (CO), 1573 (COO), 1416, 1380, 1324 (CH_2, CH_3); δ_H (400 MHz, D_2O) 3.80-3.72 (1H, m, C*H*NH_2), 1.67-1.52 (2H, m, C*H*$_2$CH), 1.48-1.28 (2H, m, CH_3C*H*$_2$) and 0.99-0.88 (3H, m, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 174.7 (*C*OOH), 54.6 (*C*HNH_2), 32.5 (*C*H_2CH), 17.8

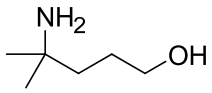
(CH_3CH_2) and 12.9 (CH_3); *m/z* 166.1 ($M + Na^+$) and 144.1 ($M + H^+$). This data is consistent with that previously reported.[343]

4-Methyl-4-nitropentan-1-ol (**3.66**)



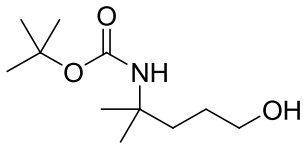
To a solution of **3.51** (31 g, 0.21 mol) in EtOH (100 mL) cooled to 0 ^oC and under N_2 was added sodium borohydride (12 g, 0.31 mol) portion wise while maintaining the temperature at 0 ^oC. After stirring at room temperature for 20 hrs, ^1H-NMR indicated complete consumption of **3.51**. The reaction mixture was cooled to 0 ^oC and carefully quenched with 10% aq. HCl (300 mL). The quenched mixture was extracted with dichloromethane and the combined organic extracts were washed with H_2O, dried over sodium sulfate, filtered and concentrated *in vacuo* to give an off white viscous oil (31 g, 0.21 mol, > 99%); υ_{max} (cm^{-1}) 3366 (OH), 2941, 2874 (CH_2, CH_3), 1532, 1472 (CNO_2), 1398, 1373 ($C(CH_3)_2$), 1347 (CNO_2), 1268, 1139, 1050 (CO), 855 (CH), 735 (CH_2); δ_H (400 MHz, $CDCl_3$) 3.70-3.07 (3H, m, C*H*$_2$O*H*), 1.87-1.69 (2H, m, C*H*$_2$$CH_2CH_2OH$), 1.43 (3H, s, CC*H*$_3$$CH_3$), 1.41 (3H, s, CCH_3C*H*$_3$) and 1.36-1.38 (2H, m, CH_2C*H*$_2$$CH_2OH$); δ_C (100 MHz, $CDCl_3$) 87.6 (*C*NO_2), 61.2 (*C*H_2OH), 36.8 (*C*$H_2CH_2CH_2OH$), 26.8 (CH_2CH_2OH) and 25.2 ($C(CH_3)_2$); *m/z* ($C_{12}H_{29}N_2O_2$ ([(2 × M) – H_2 + Na]$^+$) requires 315.1527) found 315.1527. This compound is known but has previously only been reported with ^1H NMR and IR data, which is consistent with that reported here.[344]

4-Amino-4-methylpentan-1-ol (**3.67**)



To a solution of **3.66** (1.0 g, 6.8 mmol) in MeOH (22.6 mL) stirred vigourously at 0 ^{o}C was added 6M HCl (11.3 mL, 68 mmol) followed by the cautious portion wise addition of Zn dust (8.9 g, 136 mmol). After 2 h stirring at room temperature, TLC analysis indicated the absence of the starting material and a sat. sol. of $NaHCO_3$ was added slowly (effervescence) until the *p*H of the reaction mixture was ~7. 1M NaOH was then added until the *p*H of the reaction mixture was ~12. The resulting aqueous mixture was extracted with dichloromethane (3 × 50 mL) and the organics combined, washed with sat. NaCl, dried over sodium sulfate, filtered and concentrated *in vacuo* to give a viscous clear oil which required no further purification (0.8 g, 6.7 mol, 99%); υ_{max} (cm^{-1}) 3334 (OH, NH), 3032, 2936 (CH_2, CH_3), 2873 (CNH_2), 1697, 1586, 1509 (NH_2), 1453 (CH), 1388, 1365 ($C(CH_3)_2$), 1261, 1213 (CO), 1065 (COH), 736 (CH_2); δ_H (400 MHz, $CDCl_3$) 3.51 (2H, t, *J* 5.5, C*H*$_2$OH), 2.75 (1H, br s, O*H*), 1.62-1.50 (2H, m, $CH_2CH_2CH_2CH_2OH$), 1.46-1.37 (2H, m, $CH_2CH_2CH_2CH_2OH$) and 1.08 (6H, s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 62.2 (CH_2OH), 48.5 ($C(CH_3)_2$), 41.5 ($CH_2CH_2CH_2OH$), 30.1 ($C(CH_3)_2$) and 27.5 (CH_2CH_2OH); *m*/*z* ($C_{12}H_{29}N_2O_2$ ([(2 × M) – H]$^+$) requires 233.2224) found 233.2224; 118.3 (M + H$^+$). This compound is known but has previously only been reported with ^{1}H NMR.[345]

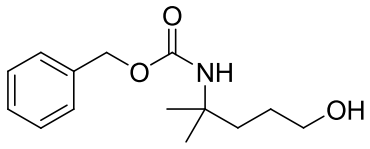
4-Methyl-4-*tert*-butyloxycarbonylamino-pentan-1-ol (**3.67-Boc**)



To a solution of **3.67** (0.12 g, 1 mmol) in acetonitrile (1 mL) at 0 ^{o}C was added di-*tert*-butyl dicarbonate (0.25 g, 1.1 mmol). The mixture was allowed to stir for 10 minutes then triethylamine (0.2 mL) was added dropwise and the reaction mixture was allowed to stir at room temperature overnight. The resulting mixture was concentrated *in vacuo* and the residues purified by silica column

chromatography (eluent; Petroleum Ether 40-60:EtOAc (7.5:2.5) to EtOAc) to give a white solid (123 mg, 0.6 mmol, 55%); υ_{max} (cm^{-1}) 3346 (OH, NH_2), 2972, 2932 (CH_2, CH_3), 2871 (CNH), 1687 (CO), 1500 (CNH), 1473, 1452 (CH), 1389, 1364 ($C(CH_3)_2$, $C(CH_3)_3$), 1274, 1252 (CO), 1165 (COH) 1051 (CO), 781, 734 (CH_2); δ_H (400 MHz, $CDCl_3$) 4.53 (1H, br s, N*H*), 3.57 (2H, t, *J* 6.5, C*H*$_2$OH), 2.49 (1H, br s, O*H*), 1.69-1.59 (2H, m, C*H*$_2$$CH_2CH_2OH$), 1.54-1.45 (2H, m, CH_2C*H*$_2$$CH_2OH$), 1.37 (9H, s, C(C*H*$_3$)$_3$) and 1.20 (6H, s, CH_2C(C*H*$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 154.7 (*C*O), 78.7 (*C*$(CH_3)_3$), 62.8 (*C*H_2OH), 52.2 (*C*$(CH_3)_2$), 36.4 (*C*$H_2CH_2CH_2OH$), 28.5 ($COOC(CH_3)_3$), 27.4 (*C*H_2CH_2OH) and 27.3 (CH_2C(*C*H_3)$_2$); *m*/*z* ($C_{11}H_{23}NNaO_3$ (M + Na^+) requires 240.1570) found 240.1571. This compound is known but has previously only been reported with ^{1}H NMR, which is consistent with that reported here.[346]

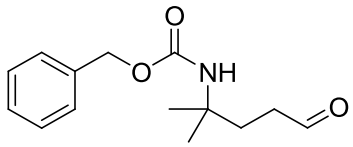
4-Carboxybenzylamino-4-methylpentan-1-ol (**3.68**)



To a solution of **3.66** (1.0 g, 6.8 mmol) in MeOH (22.6 mL) stirred vigourously at 0 ^oC was added 6M HCl (11.3 mL) followed by the cautious portion wise addition of Zn dust (8.9 g, 136 mmol). After 2 h stirring at room temperature, TLC analysis indicated the absence of the starting material and a sat. sol. of $NaHCO_3$ was added slowly (effervescence) until the *p*H of the reaction mixture was ~7. 1M NaOH was then added until the *p*H of the reaction mixture was ~12. The basic mixture was filtered to remove the solids and benzyl chloroformate (1 mL) added and allowed to stir overnight. The resulting aqueous mixture was extracted with dichloromethane and the organics combined, washed with sat. NaCl, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residues were purified by silica column chromatography (eluent; Hexane:EtOAc (4:1) to

Hexane:EtOAc (1:1)) to give a colourless oil (0.46 g, 1.8 mmol, 27%); υ_{max} (cm^{-1}) 3340 (OH), 3033, 2964, 2871 (CH_2, CH_3, OH), 1692 (CO), 1509, 1498 (CNH, Ph), 1454 (OH), 1399, 1344 ($C(CH_3)_2$), 1256, 1213 (CO), 1068, 1028 (COH), 773, 736, 696 (Ph); δ_H (400 MHz, $CDCl_3$) 7.39-7.28 (5H, m, Ph), 5.05 (2H, s, C*H*$_2$Ph), 5.00 (1H, br s, N*H*), 3.61 (2H, t, *J* 6.5, C*H*$_2$OH), 2.63 (1H, br s, O*H*), 1.78-1.66 (2H, m, C*H*$_2$$CH_2CH_2OH$), 1.60-1.50 ($CH_2$C*H*$_2$$CH_2OH$) and 1.31 (6H, s, $CH_2C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 154.6 (*C*O), 136.6 (*i*-Ph), 128.3 (Ph), 127.8 (Ph), 65.8 (*C*H_2Ph), 62.7 (*C*H_2OH), 52.4 ($C(CH_3)_2$), 36.4 (*C*$H_2CH_2CH_2OH$), 27.1 (*C*H_2CH_2OH) and 26.9 ($C(CH_3)_2$); *m*/*z* ($C_{14}H_{21}NNaO_3$ ($M + Na^+$) requires 274.1414) found 274.1414. This compound is known but has previously only been reported with ^{1}H NMR, which is consistent with that reported here.[347]

4-Carbobenzyloxyamino-4-methylpentan-1-al (**3.69**)



Method I - Swern oxidation

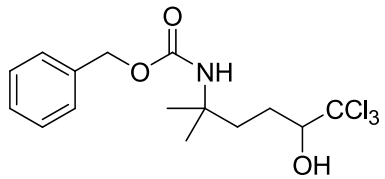
To a vacuum dried round bottom flask with a magnetic stirrer, purged with nitrogen, was added dry dichloromethane (10 mL) and a freshly opened vial of DMSO-d_6 (0.7 mL, 10 mmol). The mixture was cooled to −78 ^{o}C and oxalyl chloride (0.4 mL, 5 mmol) was added slowly to the mixture and stirred for 15 minutes before **3.68** (0.3 g, 1 mmol) in the minimum amount of dry dichloromethane was added to the reaction mixture. After 45 minutes, NEt_3 (1.4 mL, 10 mmol) was added and the reaction mixture was left stirring at room temperature overnight. The mixture was quenched with *p*H2 buffer and extracted with EtOAc, dried over sodium sulfate, filtered and concentrated *in vacuo* to give

colourless oil which was used without further purification (32 mg, 0.13 mmol, 13%).

Method II – Dess-Martin Periodinane (DMP)

To a solution of **3.68** (0.4 g, 1.6 mmol) in dichloromethane (7 mL) under nitrogen was added freshly made DMP (1.2 g, 2.8 mmol) in dichloromethane (13 mL) and allowed to stir overnight. The reaction mixture was quenched with Et_2O (150 mL) and sodium sulphite (2.8 g) in sat. $NaHCO_3$ (25 mL) was added to the mixture. The organics were separated, washed with sat. $NaHCO_3$, H_2O, dried over sodium sulfate, filtered and concentrated *in vacuo* to give a colourless oil which was used without further purification (0.4 g, 1.6, 99%); υ_{max} (cm^{-1}) 3340 (CONH), 3033 (CH_2) 2964 (CHO), 1692 (CO), 1498 (NH), 1454 (OH), 1399, 1344 ($C(CH_3)_2$), 1068, 1028 (OH), 773, 736, 696 (Ph); δ_H (400 MHz, $CDCl_3$) 9.94-10.03 (1H, m, C*H*O), 7.39-7.27 (5H, m, Ph), 5.02 (2H, s, C*H*$_2$Ph), 4.88 (1H, br s, N*H*), 2.35-2.21 (2H, m, C*H*$_2$CHO), 1.86-1.63 (2H, m, C*H*$_2$CH$_2$CHO) and 1.27 (6H, s, $CH_2C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 192.2 (*C*HO), 155.2 (*C*O), 134.3 (*i*-Ph), 129.6 (Ph), 128.8 (Ph), 128.3 (Ph), 69.5 (*C*H$_2$Ph), 53.8 ($C(CH_3)_2$), 45.7 (*C*H$_2$CHO), 27.1 ($C(CH_3)_2$) and 23.6 (*C*H$_2$CH$_2$CHO); *m*/*z* ($C_{14}H_{19}NNaO_3$ ($[M - H_2 + Na]^+$) requires 270.1101) found 270.1107. This compound has not previously been reported.

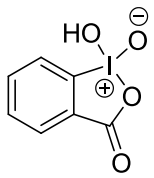
5-Carbobenzyloxyamino-5-methyl-1,1,1-trichlorohexan-2-ol (**3.70**)



Trichlorocarbinol synthesis was carried out according to **General Method J** using **3.69** (0.5 g, 2 mmol) in 2 mL of DMF. The residues were purified by silica

column chromatography (eluent; Hexane:EtOAc (9:1) to EtOAc) to give a colourless oil (86 mg, 0.2 mmol, 12%); υ_{max} (cm^{-1}) 3346 (OH, NH), 3032, 2966 (CH_2, CH_3, OH), 1702 (CO), 1586, 1499 (CNH, Ph), 1454 (OH), 1398, 1348 ($C(CH_3)_2$), 1252, 1213 (CO), 1063, 1028 (COH), 909, 824 (CCl_3), 790, 736, 696 (Ph); δ_H (400 MHz, $CDCl_3$) 7.42-7.23 (5H, m, Ph), 5.15 (2H, s, C*H*$_2$Ph), 4.65 (1H, br s, N*H*), 4.18-4.08 (1H, m, C*H*OH), 1.82-1.72 (2H, m, C*H*$_2$CH$_2$CHOH), 1.72-1.59 (2H, m, C*H*$_2$CHOH) and 1.28 (6H, s, $CH_2C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 155.1 (*C*O), 135.3 (*i*-Ph), 128.5 (Ph), 128.0 (Ph), 127.9 (*p*-Ph), 105.2 (*C*Cl_3) 88.7 (*C*H), 68.3 (*C*H_2Ph), 52.5 ($C(CH_3)_2$), 36.1 (*C*H_2CH$_2$CHOH), 27.1 ($C(CH_3)_2$) and 23.6 (*C*H_2CH$_2$OH); *m*/*z* 386.1 ($[M + NH_4 + H]^+$), 408.1 ($[M + NH_3 + Na]^+$), 297.1 ($[M - Cl_2H_2]^-$) and 265.0 ($[M - Cl_3]^-$). This compound has not previously been reported.

2-Iodoxybenzoic acid (**IBX**)



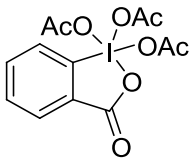
Method I - Potassium Bromate in Sulfuric Acid

To a solution of 2-iodobenzoic acid (14.2 g, 57 mmol) in 1M H_2SO_4 (89 mL) was added potassium bromate (12.6 g, 76 mmol) portion wise over a period of 30 minutes keeping the temperature below 55 ^oC with vigourous stirring. The mixture was warmed to 65 ^oC and left stirring overnight. The reaction mixture was cooled, filtered and washed with cold H_2O (200 mL) and cold EtOH (2 × 10 mL). After drying under vacuum for 2hrs, a white solid was collected (14.6 g, 52 mmol, 91%).

Method II – Oxone in water

To a solution oxone (80.5 g, 0.13 mol) in deionised H_2O (325 mL, 0.4 M) was added 2-iodobenzoic acid (25.0 g, 0.1 mol) in one portion. The reaction mixture was warmed to 73 ^oC over 20 minutes and stirred at this temperature for 3 hrs. The suspension was then cooled and left at ~ 5 ^oC for 1.5 h with slow stirring. The mixture was filtered through a sinter and the solid repeatedly washed with H_2O (6 × 100 mL) and acetone (2 × 100 mL). The white crystalline solid was left to dry in the fume hood for at least a day to give a white crystalline product (26.4 g, 94.3 mmol, 94%); m.p.: 230-231 ^oC; δ_H (400 MHz, DMSO-d_6) 8.18-8.01 (2H, m, Ph), 7.99-7.82 (2H, m, Ph); δ_C (100 MHz, DMSO-d_6) 168.6 (*C*O), 147.2 (Ph), 133.8 (Ph), 132.1 (Ph), 131.5 (Ph), 131.0 (Ph), 126.0 (Ph). This data is consistent with that previously reported.[348]

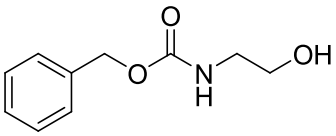
Dess-Martin periodinane (**DMP**)



An oven dried flask charged with IBX (14.6 g, 52 mmol) and AcOH (25 mL) was added Ac_2O (50 mL). The flask was purged with nitrogen and heated under stirring to 85 ^oC (internal temperature) and maintained at this temperature until all solids were consumed (~25 minutes after reaching 85 ^oC, colour change from orange to clear yellow). The reaction mixture was allowed to cool to room temperature and stirred overnight. The mixture was filtered under vacuum and the solids washed with copius amounts of diethyl ether. The residues were collected and dried under vacuum to give a crystalline white solid (12.6 g, 30 mmol, 57%); m.p.: 128-129 ^oC; δ_H (400 MHz, $CDCl_3$) 8.23-8.18 (2H, m, Ph), 8.12-8.03 (1H, m, Ph), 7.92-7.89 (1H, m, Ph), 2.32 (3H, s, CH_3), 1.95 (6H, s, 2 × CH_3); δ_C (100 MHz, $CDCl_3$) 175.9 (*C*O), 174.2 (*C*O), 166.2 (*C*O), 142.4 (*C*O),

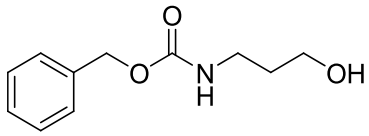
135.9 (Ph), 134.0 (Ph), 131.9 (Ph), 126.8 (Ph), 126.1 (Ph), 20.5 (*C*H_3). This data is consistent with that previously reported.[284,349]

2-Carbobenzyloxyaminoethan-1-ol (**3.83a**)



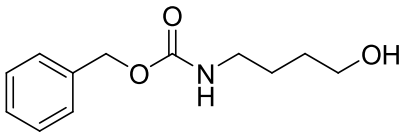
To ethanolamine (14.8 mL, 0.25 mol) in H_2O (150 mL) was simultaneously added dropwise benzyl chloroformate (35 mL, 0.25 mol) and 2M Na_2CO_3 (125 mL) over a period of 2 h while maintaining the reaction temperature at less than 8 ^oC. After complete addition, the reaction mixture was stirred at 0 ^oC for 1 hr. The mixture was extracted with EtOAc (2 × 150 mL) and the organics combined, washed with sat. aq. $NaHCO_3$, sat. aq. NaCl, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give an oil that crystallised on standing. The residues were washed with hexane, re-filtered and dried under vacuum to give a clean crystalline white solid (25.3 g, 0.13 mol, 53%); m.p.: 58-59 ^oC; υ_{max} (cm^{-1}) 3315 (OH, CONH), 2940, 2886 (CH_2), 1691 (CONH), 1541 (NH), 1452 (CH) 1267, 1213 (CO, OH), 1150 (COH), 780, 744, 694 (Ph); δ_H (400 MHz, $CDCl_3$) 7.39-7.29 (5H, m, Ph), 5.28 (1H, br s, N*H*), 5.10 (2H, s, PhCH_2), 3.69 (2H, t, *J* 5.0, CH_2OH), 3.33 (2H, t, *J* 5.0, NHCH_2) and 2.39 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 157.0 (*C*O), 136.3 (*i*-Ph), 128.4 (Ph), 128.0 (Ph), 127.9 (*p*-Ph), 66.8 (Ph*C*H_2), 61.8 (*C*H_2OH), and 43.3 (NH*C*H_2); *m*/*z* 196.1 ($M + H^+$) and 218.1 ($M + Na^+$). This data is consistent with that previously reported.[350]

3-Carbobenzyloxyaminopropan-1-ol (**3.83b**)



To a solution of 3-aminopropan-1-ol (3 mL, 40 mmol) in 1 M NaOH (44 mL, 44 mmol) with stirring at 0 ^{o}C was added benzyl chloroformate (6.3 mL, 44 mmol) dropwise over a period of 5 minutes and left stirring at 0 ^{o}C for 2 h. The mixture was then allowed to stir at room temperature for a further 1.5 h, whereupon dichloromethane (30 mL) was added and left stirring for 2 days. The dichloromethane was separated and the aqueous extracted further with dichloromethane (2 × 20 mL). The combined organics were concentrated *in vacuo* and crystallised on standing to give a white solid (8.5 g, 40 mmol, 99%); m.p.: 49-50 ^{o}C; υ_{max} (cm^{-1}) 3320 (OH, CONH), 2956, 2930, 2885, 2872 (CH_2), 1680 (CONH), 1530 (NH), 1462, 1453, 1443 (CH) 1325, 1267, 1213 (CO, OH), 1142 (COH), 1022 (CO) 773, 749 (Ph), 724 (CH_2), 697 (Ph); δ_H (400 MHz, $CDCl_3$) 7.41-7.28 (5H, m, Ph), 5.11 (2H, s, PhC*H*$_2$), 5.07 (1H, br s, N*H*), 3.67 (2H, t, *J* 5.5, C*H*$_2$OH), 3.33 (2H, dd, *J* 12.0, 6.0, NHC*H*$_2$), 2.24 (1H, br s, O*H*) and 1.70 (2H, quint, *J* 6.0, C*H*$_2$CH$_2$OH); δ_C (100 MHz, $CDCl_3$) 157.2 (*C*O), 136.4 (*i*-Ph), 128.4 (Ph), 128.1 (Ph), 128.0 (Ph), 66.7 (Ph*C*H$_2$), 59.5 (*C*H$_2$OH), 37.7 (NH*C*H$_2$) and 32.4 (NHCH$_2$*C*H$_2$); *m*/*z* 210.1 (M + H$^+$) and 232.1 (M + Na$^+$). This data is consistent with that previously reported.[351]

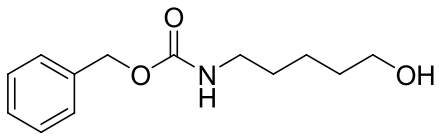
4-Carbobenzyloxyaminobutan-1-ol (**3.83c**)



To a solution of 4-aminobutan-1-ol (5 mL, 54 mmol) and NEt_3 (8.3 mL, 60 mmol) in dichloromethane (33 mL) at 0 ^{o}C was added benzyl chloroformate (8.5

mL, 60 mmol) in dichloromethane (10 mL) dropwise over a period of 10 minutes and left stirring at 0 ^{o}C for 6 h. The reaction mixture was then washed with sat. aq. NH_4Cl (2 × 25 mL) and sat. aq. NaCl (25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica column chromatography (eluent; Hexane:EtOAc (1:1) to EtOAc) to give a white crystalline solid (9.9 g, 44 mmol, 82%); m.p.: 76-77 ^{o}C; υ_{max} (cm^{-1}) 3362, 3321 (OH, CONH), 2950, 2904, 2887, 2864 (CH_2), 1683 (CONH), 1530 (NH), 1488, 1463, 1454 (CH) 1337, 1267, 1234 (CO, OH), 1137, 1104 (COH), 1056, 1010 (CO) 781, 750 (Ph), 727 (CH_2), 696 (Ph); δ_H (400 MHz, $CDCl_3$) 7.39-7.27 (5H, m, Ph), 5.09 (2H, s, PhC*H*$_2$), 4.93 (1H, br s, N*H*), 3.68-3.61 (2H, m, C*H*$_2$OH), 3.27-3.16 (2H, m, NHC*H*$_2$), 1.77 (1H, br s, O*H*) and 1.65-1.54 (4H, m, NHCH$_2$C*H*$_2$C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 156.5 (*C*O), 136.5 (*i*-Ph), 128.4 (Ph), 128.2 (*p*-Ph), 128.0 (Ph), 66.5 (Ph*C*H$_2$), 62.2 (*C*H$_2$OH), 40.7 (NH*C*H$_2$), 29.5 (NHCH$_2$*C*H$_2$) and 26.4 (*C*H$_2$CH$_2$OH); *m*/*z* 246.1 (M + Na^+). This data is consistent with that previously reported.[352]

5-Carbobenzyloxyaminopentan-1-ol (**3.83d**)



To a solution of 5-aminopentan-1-ol (3.3 mL, 30 mmol) in 3 M $NaHCO_3$ (7.6 g in 30 mL H_2O, 90 mmol) at 0 ^{o}C was added benzyl chloroformate (5.7 mL, 40 mmol) in THF (30 mL) and stirred vigourously. The reaction mixture was allowed to cool to room temperature and stirred over 2 days, whereupon the organic layer was separated and the aqueous extracted with ethyl acetate (2 × 35 mL). The organics were combined, washed with sat, aq. NaCl (100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give an oil which crystallised on standing. The residue was washed with hexane and cold Et_2O,

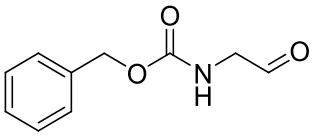
refiltered and dried under vacuum to give a clean white crystalline solid (5.0 g, 21.2 mmol, 71%); m.p.: 46-48 ^{o}C; υ_{max} (cm^{-1}) 3387, 3324 (OH, CONH), 2943, 2863 (CH_2), 1682 (CONH), 1528 (NH), 1482, 1462, 1453 (CH) 1356, 1310, 1258, 1224 (CO, OH), 1139, 1128 (COH), 1056, 1018 (CO) 783, 747 (Ph), 727 (CH_2), 696 (Ph); δ_H (400 MHz, $CDCl_3$) 7.39-7.28 (5H, m, Ph), 5.09 (2H, s, PhC*H*$_2$), 4.80 (1H, br s, N*H*), 3.63 (2H, t, *J* 6.5, C*H*$_2$OH), 3.24-3.15 (2H, m, NHC*H*$_2$), 1.63-1.48 (5H, m, NHCH$_2$C*H*$_2$CH$_2$C*H*$_2$CH$_2$O*H*) and 1.44-1.34 (2H, m, N(CH$_2$)$_2$C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 156.5 (*C*O), 136.4 (*i*-Ph), 128.4 (Ph), 128.3 (*p*-Ph), 127.9 (*p*-Ph), 66.4 (Ph*C*H$_2$), 62.2 (*C*H$_2$OH), 40.8 (NH*C*H$_2$), 32.0 (NHCH$_2$*C*H$_2$), 29.5 (NHCH$_2$CH$_2$*C*H$_2$) and 22.7 (*C*H$_2$CH$_2$OH); *m*/*z* 239.1 (M + H$_2^+$) and 260.1 (M + Na$^+$). This data is consistent with that previously reported.[353]

General Method L - Oxidation using DMP

Alcohol (1 eq) in dichloromethane (1.0 mL per mmol) was stirred at 0 ^{o}C and a solution of DMP (1.1 eq) in dichloromethane (2.5 mL per mmol) was added to the mixture and allowed to stir until the reaction was deemed complete by TLC analysis. Work up was completed in one of two ways:

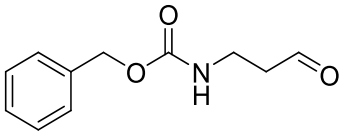
a) Diethyl ether was added to the reaction mixture and the solution poured into a sat. aq. $NaHCO_3$ solution containing 5 eq. of $Na_2S_2O_3$. The mixture was stirred for 5 minutes and the aqueous extracted with more diethyl ether. The organics were extracted and washed with sat. aq. $NaHCO_3$, H_2O, dried over sodium sulfate, filtered and concentrated *in vacuo.*
b) Diethyl ether and 1 M NaOH were added to the reaction mixture and the organic layer extracted. The organics were combined and washed with H_2O, dried over sodium sulfate, filtered and concentrated *in vacuo.*

2-Carbobenzyloxyaminoethan-1-al (**3.84a**)



Oxidation was carried out according to **General Method La** using **3.83a** (0.5 g, 2.6 mmol). The residue was purified by silica column chromatography (eluent; Hexane:EtOAc (1:1) to EtOAc) to give a white crystalline solid (0.2 g, 1.2 mmol, 45%). m.p.: 54-55 ^{o}C; υ_{max} (cm^{-1}) 3335 (CONH), 2953 (CH_2), 1686 (CONH), 1524 (NH), 1425 (CH_2) 1325, 1234, 1110 (CO), 734, 695 (Ph); δ_H (400 MHz, $CDCl_3$) 9.55 (1H, s, C*H*O), 7.37-7.27 (5H, m, Ph), 5.66 (1H, br s, N*H*), 5.11 (2H, s, PhC*H*$_2$) and 4.05 (2H, d, *J* 5.0, NHC*H*$_2$); δ_C (100 MHz, $CDCl_3$) 197.2 (*C*HO), 156.3 (O*C*O), 135.9 (*i*-Ph), 128.2 (Ph), 127.9 (Ph), 127.8 (Ph), 66.8 (Ph*C*H$_2$) and 51.1 (*C*H$_2$CHO); *m*/*z* 102.4 ([M – Bn]$^+$), 216.1 (M + Na$^+$) and 248.1 ([M + Na + O_2]$^+$). This data is consistent with that previously reported.[354]

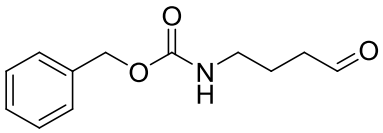
3-Carbobenzyloxyaminopropan-1-al (**3.84b**)



Oxidation was carried out according to **General Method Lb** using **3.83b** (0.5 g, 4.5 mmol). The residue was purified by silica column chromatography (eluent; Hexane:EtOAc (1:1) to EtOAc) to give a white crystalline solid (50 mg, 0.24 mmol, 10%); m.p.: 59-60 ^{o}C; υ_{max} (cm^{-1}) 3321 (CONH), 3031, 2924 (CH_2), 1681 (CONH), 1535 (NH), 1439, 1421 (CH_2) 1249, 1218, 1026 (CO), 778, 750 (Ph), 729 (CH_2), 696 (Ph); δ_H (400 MHz, $CDCl_3$) 9.78 (1H, s, C*H*O), 7.41-7.27 (5H, m, Ph), 5.24 (1H, br s, N*H*), 5.08 (2H, s, PhC*H*$_2$), 3.53-3.39 (2H, m, NHC*H*$_2$) and 2.78-2.62 (2H, m, NHC*H*$_2$CH$_2$); δ_C (100 MHz, $CDCl_3$) 199.8 (*C*HO), 156.3 (O*C*O), 136.3 (*i*-Ph), 128.5 (Ph), 128.2 (Ph), 128.1 (Ph), 66.7 (Ph*C*H$_2$), 44.2

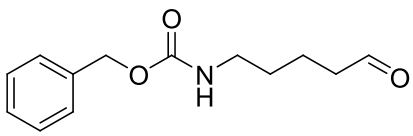
(CH_2CHO) and 34.7 ($NHCH_2$); *m*/*z* 230.1 ($M + Na^+$) and 262.1 ($[M + Na + O_2]^+$). This data is consistent with that previously reported.[355]

4-Carbobenzyloxyaminobutan-1-al (**3.84c**)



Oxidation was carried out according to **General Method La** using **3.83c** (1 g, 4.5 mmol). The residue was purified by silica column chromatography (eluent; Hexane:EtOAc (1:1) to EtOAc) to give a white crystalline solid (0.9 g, 4.2 mmol, 94%). m.p.: 46-47 ^oC; υ_{max} (cm^{-1}) 3329 (CONH), 2949 (CH_2), 1693 (CONH), 1528 (NH), 1453, 1406 (CH_2) 1252, 1212, 1105 (CO), 749, 697, 667 (Ph); δ_H (400 MHz, $CDCl_3$) 10.00 (1H, s, C*H*O), 7.38-7.27 (5H, m, Ph), 5.47 (1H, br s, N*H*), 5.08 (2H, s, PhC*H*$_2$), 3.68-3.58 (2H, m, NHC*H*$_2$), 3.26-3.07 (2H, m, C*H*$_2$CHO) and 1.62-1.47 (2H, m, $NHCH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 198.1 (*C*HO), 153.2 (O*C*O), 136.4 (*i*-Ph), 128.4 (Ph), 128.0 (Ph), 127.7 (Ph), 66.7 (Ph*C*H_2), 53.4 (*C*H_2CHO), 45.7 (NH*C*H_2) and 32.6 ($NHCH_2CH_2$); *m*/*z* 244.1 ($M + Na^+$), 246.1 ($[M + H_2 + Na]^+$) and 465.0 ($[(2 \times M) + Na]^+$). This data is consistent with that previously reported.[356]

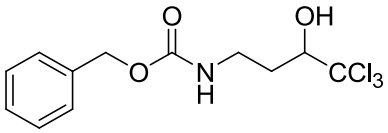
5-Carbobenzyloxyaminopentan-1-al (**3.84d**)



Oxidation was carried out according to **General Method Lb** using **3.83d** (0.5 g, 2.1 mmol). The residue was purified by silica column chromatography (eluent; Hexane:EtOAc (1:1) to EtOAc) to give a white crystalline solid (0.4 g, 1.6 mmol,

78%); m.p.: 52-53 ^{o}C; υ_{max} (cm^{-1}) 3334 (CONH), 3032, 2937 (CH_2), 1692 (CONH), 1528 (NH), 1453, 1420 (CH_2) 1252, 1133 (CO), 736, 696 (Ph); δ_H (400 MHz, $CDCl_3$) 10.00 (1H, s, C*H*O), 7.41-7.27 (5H, m, Ph), 6.12 (1H, br s, N*H*), 5.18 (2H, s, PhC*H*$_2$), 3.67-3.57 (2H, m, NHC*H*$_2$), 2.07-1.97 (2H, m, C*H*$_2$CHO), 1.87-1.73 (2H, m, C*H*$_2$CH$_2$CHO) and 1.66-1.36 (2H, m, NHCH$_2$C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 202.1 (*C*HO), 153.4 (O*C*O), 136.3 (*i*-Ph), 128.4 (Ph), 128.2 (Ph), 128.0 (Ph), 66.8 (Ph*C*H$_2$), 52.1 (*C*H$_2$CHO), 46.2 (NH*C*H$_2$), 32.6 (NHCH$_2$*C*H$_2$) and 21.9 (NHCH$_2$CH$_2$*C*H$_2$); ESI *m*/*z* 219.2 ([M – O_2]$^+$) 258.1 [M + Na$^+$) and 260.1 ([M + H_2 + Na]$^+$). This compound is known but has previously been reported without any characterisation.[357]

4-Carbobenzyloxyamino-1,1,1-trichlorobutan-2-ol (**3.85b**)

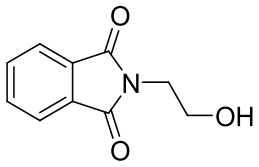


Trichlorocarbinol was synthesised according to **General Method J** using **3.84b** (50 mg, 0.24 mmol) in 1 mL of DMF. The residues were purified by silica column chromatography (eluent; Hexane:EtOAc (6:4) to EtOAc) to give a white solid (12.4 mg, 0.04 mmol, 16%); m.p.: 142-143 ^{o}C; υ_{max} (cm^{-1}) 3478 (CONH), 3230 (OH), 3098, 2962 (CH_2), 1705, 1617 (CONH), 1407, 1389, 1375 (OH), 1301, 1140 (CO), 872, 800 (CCl), 776, 713 (Ph); δ_H (400 MHz, $CDCl_3$) 7.39-7.29 (5H, m, Ph), 5.19-5.02 (3H, m, PhC*H*$_2$ & N*H*), 4.12 (1H, d, *J* 10.0 C*H*OH), 3.68-3.52 (2H, m, NHCH*H*CH$_2$CHO*H*), 3.37 (1H, dq, *J* 14.0, 5.5, NHC*H*H), 2.30 (1H, dddd, *J* 14.5, 8.0, 5.5, 2.0 NHCH$_2$C*H*HCH) and 1.84 (1H, ddd, *J* 15.0, 10.0, 5.0, NHCH$_2$CH*H*CH); δ_C (100 MHz, $CDCl_3$) 153.6 (O*C*O), 136.3 (*i*-Ph), 128.6, 128.3 (*o*-Ph & *m*-Ph), 128.1 (*p*-Ph), 104.9 (*C*Cl$_3$), 80.8 (*C*HOH), 67.0 (Ph*C*H$_2$), 37.9 (NH*C*H$_2$) and 32.1 (*C*H$_2$CHOH). This compound has not previously been reported.

General Method M - Phthalimide protection of aminoalcohol

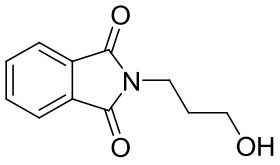
A mixture of aminoalcohol (1 eq), phthalic anhydride (1 eq), NEt_3 (0.1 eq) and toluene (1 mL per mmol) was heated under reflux in a flask fitted with a Dean-Stark apparatus for 3 hrs. The reaction mixture was allowed to cool and the remaining volatiles concentrated *in vacuo*. The solid residues were taken up in ethyl acetate and washed successively with 2M HCl, sat. aq. $NaHCO_3$ and H_2O, the organics combined and dried over sodium sulfate, filtered and concentrated *in vacuo*.

N-(2-Hydroxyethyl)-phthalimide (**3.83e**)



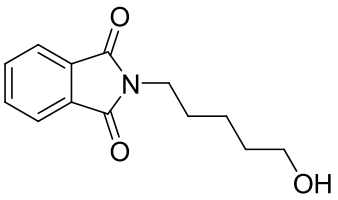
Phthalimide protection of ethanolamine (1.0 g, 16 mmol) was carried out according to **General Method M**. The crude solid was recrystallised (EtOAc:Hexane (1:1)) to give a white crystalline solid (1.5 g, 7.8 mmol, 48%); m.p.: 135-136 ^oC; υ_{max} (cm^{-1}) 3465, 3068 (OH), 3048, 2954, 2886 (CH_2), 1765, 1686 (CO), 1608 (Ph), 1469 (CH_2), 1392 (OH), 1187 (CO), 1055 (COH), 800, 722, 708 (Ph); δ_H (400 MHz, $CDCl_3$) 7.82 (2H, dd, *J* 5.5, 3.0, CCHC*H*C*H*CHC), 7.70 (2H, dd, *J* 5.5, 3.0, CC*H*CHCHC*H*C), 3.93-3.78 (4H, m, CH_2CH_2OH) and 2.57 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 168.3 (*C*O), 133.6 (CCH*C*H*C*HCHC), 131.9 ((CO)*CC*(CO)), 123.2 (C*C*HCHCHC*H*C), 61.2 (*C*H_2OH), 38.7 (NCH_2); *m*/*z* 192.1 ($M + H^+$), 214.1 ($M + Na^+$). This data is consistent with that previously reported.[358]

N-(3-Hydroxypropyl)-phthalimide (**3.83f**)



Phthalimide protection of 3-aminopropan-1-ol (2.0 g, 27 mmol) was carried out according to **General Method M**. The crude solid was recrystallised (EtOH) to give a white crystalline solid (1.9 g, 9.4 mmol, 35%); m.p.: 107-108 ^{o}C; υ_{max} (cm^{-1}) 3393 (OH), 2950, 2884 (CH_2), 1760, 1702, 1689 (CO), 1608 (Ph), 1446, 1438 (CH_2), 1399, 1374 (OH), 1124 (CO), 1059 (COH), 758, 721, 713 (Ph); δ_H (400 MHz, $CDCl_3$) 7.86 (2H, dd, *J* 5.5, 3.0, CCHC*H*C*H*CHC), 7.73 (2H, dd, *J* 5.5, 3.0, CC*H*CHCHC*H*C), 3.86 (2H, t, *J* 6.5, NC*H*$_2$), 3.66-3.57 (2H, m, C*H*$_2$OH), 2.50 (1H, br t, *J* 4.5, O*H*) and 1.88 (2H, quin, *J* 6.5, C*H*$_2$CH$_2$OH); δ_C (100 MHz, $CDCl_3$) 168.4 (*C*O), 133.7 (CCH*C*H*C*HCHC), 131.8 ((CO)*CC*(CO)), 123.0 (C*C*HCHCH*C*HC), 59.2 (*C*H$_2$OH), 38.7 (N*C*H$_2$), 31.4 (NCH$_2$*C*H$_2$); *m*/*z* 206.1 ($M + H^+$), 228.1 ($M + Na^+$). This data is consistent with that previously reported.[359]

N-(5-Hydroxypentyl)-phthalimide (**3.83h**)



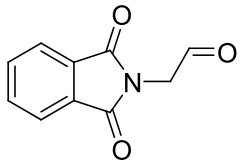
Phthalimide protection of 5-aminopentan-1-ol (4.2 mL, 39 mmol) was carried out according to **General Method M** to give **3.83** as a viscous oil (6.1 g, 26 mmol, 68%); υ_{max} (cm^{-1}) 3457 (OH), 2936, 2861 (CH_2), 1770, 1698 (CO), 1613 (Ph), 1466, 1437 (CH_2), 1395, 1364 (OH), 1126 (CO), 1049 (COH), 751, 717 (Ph); δ_H (400 MHz, $CDCl_3$) 7.76 (2H, dd, *J* 5.5, 3.0, CCHC*H*C*H*CHC), 7.65 (2H, dd, *J* 5.5, 3.0, CC*H*CHCHC*H*C), 3.67-3.53 (4H, m, NC*H*$_2$(CH$_2$)$_3$C*H*$_2$OH), 2.82 (1H,

br s, O*H*), 1.70-1.61 (2H, m, NCH_2CH_2), 1.60-1.51 (2H, m, CH_2CH_2OH) and 1.43-1.31 (2H, m, $NCH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 168.4 (*C*O), 133.8 (CCH*C*H*C*HCHC), 131.9 ((CO)*CC*(CO)), 123.0 (C*C*HCHCH*C*HC), 62.3 (CH_2OH), 37.7 (NCH_2), 32.0 (NCH_2CH_2), 28.2 (CH_2CH_2OH), 22.9 ($CH_2CH_2CH_2OH$); *m*/*z* 234.1 ($M + H^+$), 256.1 ($M + Na^+$). This data is consistent with that previously reported.[360]

General Method N - Oxidation of alcohol with IBX

Alcohol (1 eq) in ethyl acetate (4.0 mL per mmol) was added IBX (2 eq) and stirred under nitrogen at reflux until TLC analysis showed the completion of reaction. The reaction mixture was allowed to cool to room temperature and the cloudy mixture filtered through a thin pad of celite and the filter cake washed with copious amounts of ethyl acetate into a round bottomed flask. The filtrate was concentrated *in vacuo.*

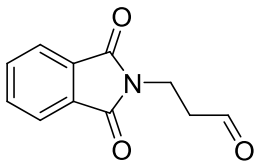
N-(2-Oxoethyl)-phthalimide (**3.84e**)



Oxidation was carried out according to **General Method N** using **3.83e** (1.5 g, 7.8 mmol) to give a white solid which required no further purification (97 mg, 5.1 mmol, 66%); m.p.: 114-115 ^oC; υ_{max} (cm^{-1}) 3049, 2938 (CH_2), 1777, 1705 (CO), 1614 (Ph), 1406 (CH_2), 1191, 1140 (CO), 774, 726, 713 (Ph); δ_H (400 MHz, $CDCl_3$) 9.69 (1H, s, C*H*O), 7.90 (2H, dd, *J* 5.5, 3.0, CCHC*H*C*H*CHC), 7.76 (2H, dd, *J* 5.5, 3.0, CC*H*CHCHC*H*C) and 4.56 (2H, s, CH_2CHO); δ_C (100 MHz, $CDCl_3$) 193.7 (*C*HO), 167.3 (*C*O), 134.1 (CCH*C*H*C*HCHC), 131.6

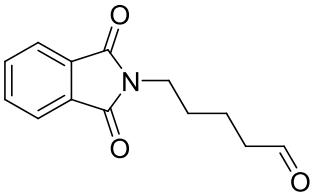
((CO)*CC*(CO)), 123.4 (C*C*HCHCHC*C*HC), 47.1 (*C*H_2); *m*/*z* 190.1 (M + H^+), 212.1 (M + Na^+), 244.0 ([M + MeOH + Na]$^+$) and 276.1 ([M + (2 × MeOH) + Na]$^+$). This data is consistent with that previously reported.[358]

N-(3-Oxopropyl)-phthalimide (**3.84f**)



Oxidation was carried out according to **General Method N** using **3.83f** (1.5 g, 7.3 mmol) to give a white solid which required no further purification (97 mg, 4.8 mmol, 65%); m.p.: 126-127 ^oC; υ_{max} (cm^{-1}) 3051, 2928 (CH_2), 2850 (NCH_2), 1765, 1701 (CO), 1610 (Ph), 1470, 1440 (CH_2), 1188, 1135 (CO), 800, 739, 719 (Ph); δ_H (400 MHz, $CDCl_3$) 9.82 (1H, s, C*H*O), 7.85 (2H, dd, *J* 5.5, 3.0, CCHC*H*C*H*CHC), 7.73 (2H, dd, *J* 5.5, 3.0, CC*H*CHCHC*H*C), 4.04 (2H, t, *J* 7.0, NC*H*$_2$) and 2.88 (2H, dt, *J* 7.0, 1.5, C*H*$_2$CHO); δ_C (100 MHz, $CDCl_3$) 199.7 (*C*HO), 168.3 (*C*O), 134.3 (CCH*C*H*C*HCHC), 131.9 ((CO)*CC*(CO)), 122.4 (C*C*HCHCH*C*HC), 42.5 (*C*H_2CHO), 32.0 (NCH_2); *m*/*z* 204.1 (M + H^+), 226.0 (M + Na^+), 258.1 ([M + MeOH + Na]$^+$) and 290.1 ([M + (2 × MeOH) + Na]$^+$). This data is consistent with that previously reported.[359]

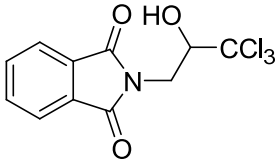
N-(5-Oxopentyl)-phthalimide (**3.84h**)



Oxidation was carried out according to **General Method N** using **3.83h** (1.5 g, 6.4 mmol) to give a colourless oil which required no further purification (1.1 g,

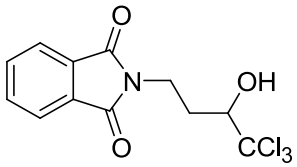
5.0 mmol, 77%); υ_{max} (cm^{-1}) 3045, 2918 (CH_2), 2848 (NCH_2), 1764, 1703 (CO), 1609 (Ph), 1465, 1434 (CH_2), 1192, 1137 (CO), 742, 718 (Ph); δ_H (400 MHz, $CDCl_3$) 9.66-9.63 (1H, m, C*H*O), 7.73 (2H, dd, *J* 5.5, 3.0, CCHC*H*C*H*CHC), 7.60 (2H, dd, CC*H*CHCHC*H*C), 3.59 (2H, t, *J* 7.0, NC*H*$_2$), 2.40 (2H, t, *J* 7.0, C*H*$_2$CHO) and 1.70-1.50 (4H, m, $NCH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 202.1 (*C*HO), 168.7 (*C*O), 134.1 (CCH*C*H*C*HCHC), 132.2 ((CO)*CC*(CO)), 123.5 (C*C*HCHCH*C*HC), 43.6 (*C*H_2CHO), 37.9 (N*C*H_2), 28.4 (NCH_2CH_2), 19.2 (CH_2CH_2CHO); *m*/*z* 232.1 ($M + H^+$), 254.1 ($M + Na^+$). This data is consistent with that previously reported.[361]

N-(2-Hydroxy-3,3,3-trichloropropyl)-phthalimide (**3.85e**)



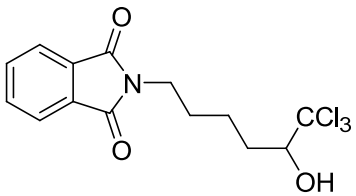
Trichlorocarbinol was synthesised according to **General Method J** using **3.84e** (1.0 g, 5.1 mmol) in 5 mL of DMF. The residues were purified by silica column chromatography (eluent; Hexane:EtOAc (6:4) to EtOAc) to give a white solid (0.7 g, 2.2 mmol, 43%); m.p.: 138-139 ^oC; υ_{max} (cm^{-1}) 3446 (OH), 2953, 2922 (CH_2), 1780, 1701 (CON), 1618 (Ph) 1466 (CH_2), 1399 (OH), 1288, 1194 (CO), 1143, 1099 (COH), 787 (CCl), 723, 711 (Ph); δ_H (400 MHz, $CDCl_3$) 7.86 (2H, dd, *J* 5.5, 3.0, CCHC*H*C*H*CHC), 7.74 (2H, dd, *J* 5.5, 3.0, CC*H*CHCHC*H*C), 4.46 (1H, ddd, *J* 9.5, 7.5, 3.0, CH_2CHOH), 4.33 (1H, dd, *J* 14.5, 3.0, NC*H*HCH), 4.09 (1H, dd, *J* 14.5, 9.5, NCH*H*CH) and 3.60 (1H, d, *J* 7.5, CHO*H*); δ_C (100 MHz, $CDCl_3$) 168.4 (*C*O), 134.3 (Ph), 131.7 (Ph), 123.6 (Ph), 100.8 (*C*Cl_3), 80.0 (CH_2CH) and 39.8 (*C*H_2); *m*/*z* ($C_{11}H_9Cl_3NO_3$ ($M + H^+$) requires 307.9643 and 309.9613) found 307.9650 and 309.9617. This compound has not previously been reported.

N-(3-Hydroxy-4,4,4-trichlorobutyl)-phthalimide (**3.85f**)



Trichlorocarbinol was synthesised according to **General Method J** using **3.84f** (1.0 g, 4.8 mmol) in 5 mL of DMF. The residues were purified by dissolving in the minimum amount of chloroform and washing with H_2O. The organic extract was dried again with sodium sulfate, filtered and concentrated *in vacuo* to give a clean white solid (1.2 g, 3.7 mmol, 76%); m.p.: 156-157 ^oC; υ_{max} (cm^{-1}) 3327 (OH), 2979, 2946, (CH_2), 2855 (NCH_2) 1767, 1692 (CON), 1612 (Ph) 1468, 1439 (CH_2), 1397 (OH), 1281, 1227 (CO), 1189, 1091 (COH), 779 (CCl), 716 (Ph); δ_H (400 MHz, $CDCl_3$) 7.86 (2H, dd, *J* 5.5, 3.0, CCHC*H*C*H*CHC), 7.73 (2H, dd, *J* 5.5, 3.0, CC*H*CHCHC*H*C), 4.11 (1H, m, CH_2C*H*OH), 3.97 (2H, dd, *J* 7.0, 5.5, NCH_2), 3.59 (1H, br s, CHO*H*), 2.44 (1H, dtd, *J* 9.0, 7.0, 2.0, NCH_2C*H*HCH) and 2.05 (1H, m, NCH_2CH*H*CH); δ_C (100 MHz, $CDCl_3$) 168.4 (*C*O), 134.2 (Ph), 131.9 (Ph), 123.4 (Ph), 103.1 (*C*Cl_3), 80.7 (CH_2*C*HOH), 34.9 (N*C*H_2) and 30.8 (*C*H_2CH); *m*/*z* ($C_{12}H_{10}Cl_3NO_3$ ($M + H^+$) requires 321.9799, 323.9770 and 325.9740) found 321.9803, 323.9773 and 325.9741. This compound has not previously been reported.

N-(5-Hydroxy-6,6,6-trichlorohexyl)-phthalimide (**3.85h**)

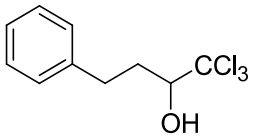


Trichlorocarbinol was synthesised according to **General Method J** using **3.84h** (1.2 g, 5 mmol) in 5 mL of DMF. The residues were purified by silica column

chromatography (eluent; Hexane:EtOAc (8:2) to EtOAc) to give a white solid (0.8 g, 2.2 mmol, 44%); m.p.: 131-133 ^{o}C; υ_{max} (cm^{-1}) 3425 (OH), 2954, 2933, (CH_2), 2865 (NCH_2) 1765, 1700 (CON), 1608 (Ph) 1460, 1434 (CH_2), 1398 (OH), 1263, 1245 (CO), 1185, 1090 (COH), 792 (CCl), 771, 717 (Ph); δ_H (400 MHz, $CDCl_3$) 7.85 (2H, d, *J* 5.5, 3.0, CCHC*H*C*H*CHC), 7.72 (2H, dd, *J* 5.5, 3.0, CC*H*CHCHC*H*C), 3.99 (1H, ddd, *J* 9.5, 6.0, 2.0 CH_2C*H*OH), 3.74 (2H, t, *J* 7.0, NC*H*$_2$), 2.85 (1H, dd, *J* 6.0, 1.0, CHO*H*), 2.16-2.06 (1H, m, NCH_2C*H*H), 1.86-1.63 (4H, m, NCH_2CH*H*C*H*HC*H*$_2$CH) and 1.57-1.47 (1H, m, NCH_2CH_2CH*H*); δ_C (100 MHz, $CDCl_3$) 168.5 (*C*O), 134.0 (*m*-Ph), 132.1 (*i*-Ph), 123.2 (*o*-Ph), 82.7 (CH_2*C*HOH), 37.5 (N*C*H_2), 30.8 (NCH_2*C*H_2), 28.2 (*C*H_2CH) and 23.2 (N(CH_2)$_2$*C*H_2). This compound has not previously been reported.

5.4 Chapter 4 Experimental

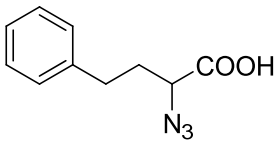
1,1,1-Trichloro-4-phenylbutan-2-ol (**4.12**)



Trichlorocarbinol was synthesised according to **General Method J** using **4.11** (6.6 mL, 50 mmol). The residues were purified by silica column chromatography (eluent; EtOAc:Hexane (0.5:9.5) to EtOAc) to give a light yellow oil (8.1 g, 32 mmol, 63%); υ_{max} (cm^{-1}) 3414, 3062 (OH), 2934, 2862 (CH_2, CH), 1602, 1496 (Ph), 1454 (CH_2), 1095, 1075, 1055 (COH), 807, 785 (CCl), 745, 697 (Ph); δ_H (400 MHz, $CDCl_3$) 7.39-7.32 (2H, m, *m*-Ph), 7.31-7.22 (3H, m, *o*-Ph & *p*-Ph), 4.02 (1H, ddd, *J* 10.0, 5.0, 1.0, C*H*OH), 3.04 (1H, ddd, *J* 14.0, 9.0, 5.0, C*H*HCHOH), 2.90 (1H, br s, O*H*), 2.81 (1H, dt, *J* 14.0, 8.5, C*H*HCH$_2$CH), 2.42 (1H, dt, *J* 14.0, 9.0, C*H*HCH$_2$CH) and 2.03 (1H, dddd, *J* 14.0, 10.0, 9.0, 5.0, C*H*HCHOH); δ_C (100 MHz, $CDCl_3$) 140.7 (*i*-Ph), 128.5 (Ph), 128.4 (Ph), 126.2 (*p*-Ph), 104.1 (*C*Cl_3), 81.9 (*C*H), 32.9 (*C*H_2CH_2CH) and 31.9 (*C*H_2CH); *m*/*z*

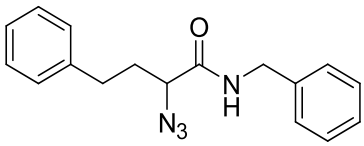
147.1 ([M – $HCCl_3$ + H]$^+$), 169.1 ([M – $HCCl_3$ + Na]$^+$). This data is consistent with that previously reported.[259]

2-Azido-4-phenylbutanoic acid (**4.13**)



Azido acid was synthesised according to **General Method K** using **4.12** (253 mg, 1 mmol) to give a viscous clear liquid (196 mg, 0.96 mmol, 96%); υ_{max} (cm^{-1}) 3027 (OH), 2929 (CH_2), 2103 (N_3), 1713 (CO_2H), 1603, 1496 (Ph), 1454 (CH_2), 1225, 1030 (CO), 748, 697 (Ph); δ_H (400 MHz, $CDCl_3$) 11.15 (1H, br s, COO*H*), 7.36-7.16 (5H, m, Ph), 3.88 (1H, dd, *J* 9.0, 5.0, C*H*N_3), 2.83 (1H, ddd, *J* 9.0, 7.0, 4.0, PhC*H*HCH_2), 2.73 (1H, dd, *J* 14.0, 9.0, PhCH*H*CH_2), 2.28-2.01 (2H, m, PhCH_2C*H*$_2$CH); δ_C (100 MHz, $CDCl_3$) 176.4 (*C*OOH), 139.7 (*i*-Ph), 128.6 (Ph), 128.4 (Ph), 126.4 (*o*-Ph), 60.9 (*C*HN_3), 32.7 (Ph*C*H_2), 31.6 (CH_2*C*H_2CH); *m*/*z* ($C_{10}H_{12}N_3O_2$ (M + H$^+$) requires 206.0924) found 206.0924). This compound is known but has previously been reported without any characterisation.[362]

2-Azido-*N*-benzyl-4-phenylbutanamide (**4.14**)



Method A

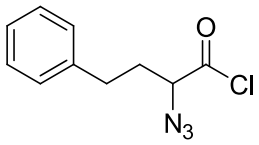
To a solution of **4.12** (253 mg, 1 mmol) in 1,2-dimethoxyethane (160 µL, 1.5 mmol) and benzylamine (110 µL, 1 mmol) stirred at 10 ^oC was added a stirred 10

^{o}C solution of NaN_3 (130 mg, 2 mmol) and NaOH (160 mg, 4 mmol) in H_2O (8 mL). The mixture was brought to room temperature and left stirring overnight. The remaining solution was extracted with EtOAc, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residues were purified by silica column chromatography (eluent; Petroleum Ether 40/60 ^{o}C to EtOAc) to give a white solid (68 mg, 0.23 mmol, 23%). m.p.: 60-61 ^{o}C; υ_{max} (cm^{-1}) 3297 (NH), 3027, 2930 (CH_2), 2109, 2090 (N_3), 1644 (CONH), 1605 (Ph), 1542 (CONH), 1452 (CH_2), 744, 695 (Ph); δ_H (400 MHz, $CDCl_3$) 7.39-7.19 (10H, m, Ph), 6.69 (1H, br s, CON*H*), 4.48 (1H, dd, *J* 13.0, 4.0, CONHCH*H*Ph), 4.44 (1H, dd, *J* 13.0, 4.0, CONHC*H*HPh), 4.01 (1H, dd, *J* 7.5, 4.5, C*H*N_3), 2.80 (1H, dt, *J* 14.0, 5.0, PhC*H*HCH_2), 2.70-2.78 (1H, m, PhCH*H*CH_2), 2.29 (1H, dddd, *J* 14.0, 9.5, 7.0, 5.0, PhCH_2C*H*HCH) and 2.17 (1H, dddd, *J* 14.0, 9.0, 7.5, 6.0, PhCH_2CH*H*CH); δ_C (100 MHz, $CDCl_3$) 169.0 (*C*O), 140.2 (CONHCH_2(*i*-Ph)), 137.6 (CH_2CH_2(*i*-Ph)), 128.8 (Ph), 128.5 (Ph), 128.4 (Ph), 127.73 (Ph), 127.68 (CONHCH_2(*p*-Ph)), 126.3 (CH_2CH_2(*p*-Ph)), 63.6 (*C*HN_3), 43.5 (CONH*C*H_2Ph), 33.9 (*C*H_2CHN_3) and 31.4 (Ph*C*H_2CH_2); *m*/*z* ($C_{17}H_{18}N_4O$ ($[M + H]^+$) requires 295.1553) found 295.1550 and ($C_{17}H_{18}N_4NaO$ ($[M + Na]^+$) requires 317.1373) found 317.1368. This compound has not previously been reported.

Method B

To a solution of **4.16** (53 mg, 0.23 mmol) in dihcloromethane (3 mL) was added benzylamine (100 µL, 0.9 mmol) and the resulting solution left stirring overnight. The remaining residues were taken up in *p*H 2 buffer and extracted with EtOAc, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residues were purified by silica column chromatography (eluent; Hexane:EtOAc (4:1)) to give a white solid (**4.14**, 61 mg, 0.2 mmol, 86%). The spectral data was identical to that obtained from Method A.

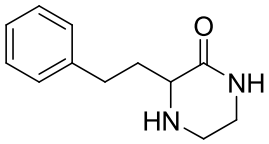
2-Azido-4-phenylbutanoyl chloride (**4.16**)



Oxalyl chloride (90 µL, 1 mmol) and DMF (20 µL, 0.23 mmol) were added to a 0.23M solution of 2-azido-4-phenylbutanoic acid (48 mg, 0.23 mmol) in hexanes. The reaction mixture was stirred at room temperature until TLC showed consumption of the starting material (3 h). The reaction mixture was filtered and concentrated *in vacuo* and the acid chloride (**4.16**) was used without isolation or further purificiation.

General Method O: Heterocycle formation *via* Jocic/Bargellini type reaction

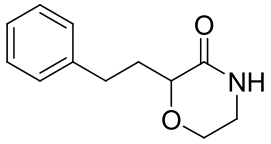
3-Phenylethylpiperazin-2-one (**4.17**)



To a solution of 1,1,1-Trichloro-4-phenylbutan-2-ol (**4.12**, 0.25 g, 1 mmol) and benzyltriethylammoniumchloride (5 mg, 2 mol %) in dichloromethane (10 mL) stirred at 0 ^{o}C was added ethylenediamine (67 µL, 1 mmol). The mixture was allowed to stir for 10 minutes, followed by dropwise addition of 40 % aq. NaOH (0.25 mL). Stirring was continued overnight at room temperature. The reaction mixture was quenched with H_2O until all of the solids were consumed and the aqueous was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo.* The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:1) to EtOAc:MeOH (8:2)) to give a white crystalline solid (113 mg, 0.6 mmol, 55%); m.p.: 146-147 ^{o}C; υ_{max} (cm^{-1}) 3331 (NH), 3252 (CONH), 2962, 2913,

2853 (CH_2, CH), 1654, 1620 (CONH), 1494 (NH), 1452, 1396 (CH_2), 759 (Ph), 747 (CH_2), 702 (Ph); δ_H (400 MHz, $CDCl_3$) 7.31-7.14 (5H, m, Ph), 6.55 (1H, br s, CON*H*), 3.46-3.36 (2H, m, C*H*CONHC*H*H), 3.32-3.34 (1H, m, CONHCH*H*), 3.13 (1H, dtd, *J* 13.0, 4.0, 0.5, CHNHC*H*H), 2.96 (1H, dddd, *J* 13.0, 9.5, 4.0, 2.0, CHNHCH*H*), 2.85-2.68 (2H, m, C$H_2$$CH_2$CH), 2.35-2.24 (1H, m, C*H*HCHNH), 2.04-1.91 (1H, m, CH*H*CHNH), and 1.90 (1H, br s, CHN*H*); δ_C (100 MHz, $CDCl_3$) 172.3 (CO), 141.5 (*i*-Ph), 128.5, 128.4 (*o*- & *m*-Ph), 125.9 (*p*-Ph), 58.3 (*C*H), 43.2 (CONH*C*H_2), 41.4 (CHNH*C*H_2), 33.6 (*C*H_2CHNH) and 32.1 (*C*$H_2$$CH_2$CH); *m*/*z* ($C_{12}H_{17}N_2O$ (M + H^+) requires 205.1335) found 205.1335. This compound is known but has previously been reported without any characterisation.[363]

2-Phenylethylmorpholin-3-one (**4.19**)

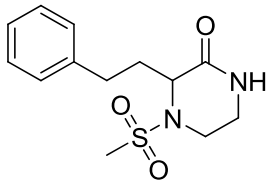


Heterocycle formation was carried out according to **General Method O** using ethanolamine (61 µL, 1 mmol) in place of ethylenediamine. The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (9:1) to EtOAc:MeOH (8:2)) to give a viscous oil (91 mg, 0.44 mmol, 44 %); υ_{max} (cm^{-1}) 3383 (CONH), 2960, 2849 (CH_2, CH), 2258 (CON), 1654 (CONH), 1047, 1023 (CO), 763, 699 (Ph); δ_H (400 MHz, $CDCl_3$) 7.33-7.27 (2H, m, *m*-Ph), 7.25-7.18 (3H, m, *o*- & *p*-Ph), 7.00 (1H, br s, CON*H*), 4.32 (1H, dd, *J* 9.0, 4.0, C*H*OCH_2), 3.75 (2H, t, *J* 5.0, OC$H_2$$CH_2$NH), 3.50-3.42 (2H, m, O$CH_2CH_2$NH), 2.92-2.73 (2H, m, PhCH_2), 2.47 (1H, dddd, *J* 14.5, 9.5, 7.0, 4.0, PhCH_2C*H*HCH) and 2.30-1.90 (2H, m, PhCH_2CH*H*CHN*H*); δ_C (100 MHz, $CDCl_3$) 169.8 (CO), 140.0 (*i*-Ph), 128.6, 128.5 (*o*- & *m*-Ph), 126.3 (*p*-Ph), 61.9 (CHO*C*H_2), 60.3 (*C*H), 42.5 (CONH*C*H_2), 37.0 (PhCH_2*C*H_2CH) and 31.9 (Ph*C*$H_2$$CH_2$CH); *m*/*z* ($C_{12}H_{16}NO_2$

($M + H^+$) requires 206.1176) found 206.1178. This compound has not previously been reported.

General Method P: Amine alkylation with acid chloride

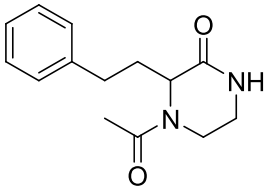
4-(Methylsulfonyl)-3-phenylethylpiperazin-2-one (**4.20**)



To a solution of **4.17** (14 mg, 0.07 mmol) in dry dichloromethane (2 mL) stirred at 0 ^oC was added NEt_3 (9 µL, 0.07 mmol) and stirred for 10 minutes, after which time methanesulfonyl chloride (10 µL, 0.14 mmol) was added slowly and left stirring until the complete consumption of the starting material was observed by TLC. The reaction mixture was concentrated *in vacuo* and *p*H 2 buffer added to the residues. The aqueous mixture was extracted with EtOAc and the combined organic extracts dried over sodium sulfate, filtered and concentrated *in vacuo*. The residues were purified by silica column chromatography (eluent; EtOAc:Petroleum Ether 40/60 ^oC (2:8) to EtOAc) to give a white crystalline solid (6 mg, 0.02 mmol, 31%); m.p.: 168-169 ^oC; υ_{max} (cm^{-1}) 3175, 3031 (NH), 2931 (CH_2), 1661 (CONH), 1603, 1494 (Ph), 1454, 1429 (CH_2), 1370 (CH_3) 1317, 1141 (SO_2N), 773, 702 (Ph); δ_H (400 MHz, $CDCl_3$) 7.32-7.26 (2H, m, *m*-Ph), 7.25-7.16 (3H, m, Ph), 6.46 (1H, br s, CON*H*), 4.32 (1H, dd, *J* 9.0, 5.0, C*H*CONH), 3.91 (1H, dd, *J* 14.0, 4.0, $CONHCH_2CH\mathit{H}$), 3.65 (1H, dt, *J* 12.0, 4.5, CONHCH*H*), 3.45 (1H, ddd, *J* 14.0, 11.0, 4.0, $CONHCH_2C\mathit{H}H$), 3.39-3.31 (1H, m, CONHC*H*H), 2.93 (3H, s, CH_3), 2.89-2.75 (2H, m, $PhCH_2CH_2$), 2.34 (1H, dddd, *J* 11.5, 10.0, 6.5, 5.0, $PhCH_2C\mathit{H}H$) and 2.16-2.06 (1H, m, $PhCH_2CH\mathit{H}$); δ_C (100 MHz, $CDCl_3$) 140.6 (*i*-Ph), 128.5 (Ph), 128.4 (Ph), 126.2 (*p*-Ph), 57.8 (*C*H), 41.23 ($CONHCH_2$), 40.1 (CH_3), 38.5 ($CONHCH_2CH_2$), 33.9 (CH_2CHCO) and

32.3 (*C*H_2CH_2CH); *m*/*z* ($C_{13}H_{18}N_2NaO_3S$ (M + Na^+) requires 305.0930) found 205.0931. This compound has not previously been reported.

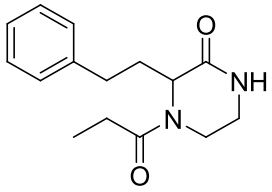
4-Acetyl-3-phenylethylpiperazin-2-one (**4.21**)



Amine alkylation was carried out according to **General Method P** using **4.17** (10 mg, 0.05 mmol) and acetyl chloride (4 µL, 0.06 mmol). The residue was purified by silica column chromatography (eluent; EtOAc to EtOAc:MeOH (8:2)) to give a white crystalline solid (11 mg, 0.04 mmol, 88%); m.p.: 147-148 ^oC; υ_{max} (cm^{-1}) 3282 (NH), 3030, 2920, 2851 (CH_2, CH), 1659 (CON), 1605 (CONH), 1481 (Ph), 1439, 1426 (CH_2), 1338 (CH_3), 740 (Ph), 720 (CH_2), 702 (Ph); δ_H (400 MHz, 1.3:1 rotamer ratio, $CDCl_3$) $^{mj\ \&\ mi}$7.34-7.14 (2 × 5H, m, Ph), ^{mi}6.68 (1H, br s, CON*H*), ^{mj}6.41 (1H, br s, CON*H*), ^{mi}5.19 (1H, dd, *J* 9.0, 5.0, C*H*CONH), ^{mj}4.73-4.65 (1H, m, CHNC*H*H), ^{mj}4.32-4.26 (1H, m, C*H*CONH), ^{mi}3.79-3.69 (1H, m, CHNC*H*H), 3.54-3.40 (3H, m, ^{mi}CONHCH*HC*H*H* & ^{mj}CONHCH*H*), ^{mi}3.37-3.31 (1H, m, CONHC*H*H), ^{mj}3.30-3.22 (1H, m, CONHC*H*H), ^{mj}3.10-2.99 (1H, m, CHNCH*H*), 2.87-2.73 (3H, m, ^{mj}PhCH_2CH_2CH & ^{mi}PhC*H*HCH_2CH), ^{mi}2.71-2.60 (1H, m, PhCH*H*CH_2CH), ^{mj}2.48-2.37 (1H, m, PhCH_2C*H*HCH), ^{mi}2.37-2.27 (1H, m, PhCH_2C*H*HCH), ^{mj}2.12 (3H, s, CH_3CO), 2.09-1.99 (2H, m, ^{mj}PhCH_2CH*H*CH & ^{mi}PhCH_2CH*H*CH) and ^{mi}1.93 (3H, s, CH_3CO); δ_C (100 MHz, $CDCl_3$) ^{mj}140.1 (*i*-Ph), ^{mi}135.1 (*i*-Ph), ^{mj}128.6 (Ph), ^{mj}128.4 (Ph), ^{mi}128.30 (Ph), ^{mi}128.25 (Ph), ^{mj}126.4 (*p*-Ph), ^{mi}125.9 (*p*-Ph), ^{mj}58.5 (*C*H), ^{mi}55.0 (*C*H), 41.6, 41.0, 40.2 , 34.6 (CONH*C*H_2*C*H_2), 34.1, 33.2, 32.4, 32.1 (Ph*C*H_2*C*H_2), ^{mj}30.9 (CH_3) and ^{mi}21.0 (*C*H_3); *m*/*z*

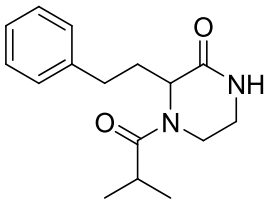
($C_{14}H_{18}N_2NaO_2$ (M + Na^+) requires 269.1260) found 269.1260. This compound has not previously been reported.

3-Phenylethyl-4-propionylpiperazin-2-one (**4.22**)



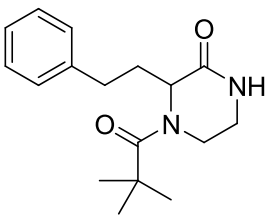
Amine alkylation was carried out according to **General Method P** using **4.17** (10 mg, 0.05 mmol) and propionyl chloride (5 μL, 0.06 mmol). The residue was purified by silica column chromatography (eluent; EtOAc to EtOAc:MeOH (9:1)) to give a white crystalline solid (10 mg, 0.04 mmol, 82%); m.p.: 184-186 ^oC; υ_{max} (cm^{-1}) 3229 (NH), 3026, 2918 (CH_2, CH), 1638 (CON), 1490 (Ph), 1422 (CH_2), 1326 (CH_3) 750, 700 (Ph); δ_H (400 MHz, 1.1:1 rotamer ratio, $CDCl_3$) $^{mj\ \&}$ ^{mi}7.34-7.13 (2 × 5H, m, Ph), ^{mi}6.45 (1H, br s, CON*H*), ^{mj}6.21 (1H, br s, CON*H*), ^{mi}5.25-5.19 (1H, m, C*H*CONH), ^{mj}4.75-4.67 (1H, m, CHNC*H*H), ^{mj}4.34 (1H, t, *J* 7.0, C*H*CONH), ^{mi}3.85-3.75 (1H, m, CHNC*H*H), 3.52-3.39 (3H, m, ^{mi}CONHCH*HC*H*H* & ^{mj}CONHCH*H*), ^{mi}3.36-3.31 (1H, m, CONHC*H*H), ^{mj}3.30-3.22 (1H, m, CONHC*H*H), ^{mj}3.11-3.00 (1H, m, CHNCH*H*), 2.88-2.72 (3H, m, ^{mj}PhC*H*$_2$CH$_2$CH & ^{mi}PhC*H*HCH$_2$CH), ^{mi}2.70-2.59 (1H, m, PhCH*H*CH$_2$CH), ^{mj}2.48-2.38 (1H, m, PhCH$_2$C*H*HCH), ^{mi}2.38-2.26 (3H, m, PhCH$_2$C*H*HCH & CH$_3$C*H*$_2$), 2.24-1.97 (4H, m, ^{mj}PhCH$_2$CH*H*CH, ^{mi}PhCH$_2$CH*H*CH & ^{mj}CH$_3$C*H*$_2$), ^{mi}1.18 (3H, t, *J* 7.5 C*H*$_3$CH$_2$) and ^{mj}1.08 (3H, t, *J* 7.5 C*H*$_3$CH$_2$); δ_C (100 MHz, $CDCl_3$) ^{mj}128.6 (Ph), ^{mj}128.4 (Ph), ^{mi}128.29 (Ph), ^{mi}128.26 (Ph), ^{mj}126.4 (*p*-Ph), ^{mi}125.9 (*p*-Ph), ^{mj}57.6 (*C*H), ^{mi}55.2 (*C*H), 41.7, 41.1, 39.2, 34.7 (CONH*C*H$_2$*C*H$_2$), 34.2, 33.3, 32.4, 32.1 (Ph*C*H$_2$*C*H$_2$), ^{mi}26.6 (CH$_3$*C*H$_2$), ^{mj}25.9 (CH$_3$*C*H$_2$), ^{mj}9.30 (*C*H$_3$CH$_2$) and ^{mi}9.27 (*C*H$_3$CH$_2$); *m*/*z* ($C_{15}H_{20}N_2NaO_2$ (M + Na^+) requires 283.1417) found 283.1419. This compound has not previously been reported.

4-Isobutyryl-3-phenylethylpiperazin-2-one (**4.23**)



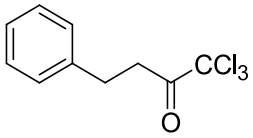
Amine alkylation was carried out according to **General Method P** using **4.17** (10 mg, 0.05 mmol) and isobutyryl chloride (6 µL, 0.06 mmol). The residue was purified by silica column chromatography (eluent; EtOAc to EtOAc:MeOH (9:2)) to give a white crystalline solid (1.2 mg, 0.004 mmol, 9%); m.p.: 171-172 ^{o}C; υ_{max} (cm^{-1}) 3259 (NH), 3026, 2919, 2850 (CH_2, CH), 1633 (CON), 1545 (NH), 1494 (Ph), 1427 (CH_2), 1332 (CH_3) 746, 699 (Ph); δ_H (400 MHz, rotamer ratio 2:1, $CDCl_3$) $^{mj\ \&\ mi}$7.36-7.15 (2 × 5H, m, Ph), ^{mj}5.24 (1H, t, *J* 7.0, CH_2CH), ^{mi}4.44 (1H, t, *J* 7.0, CH_2CH), ^{mi}4.30-4.19 (1H, m, CHNC*H*H), 3.98-3.56 (7H, m, $^{mj}NCH_2CH_2NH$, $^{mj}N(CO)CH$, $^{mi}NHCH_2$), ^{mi}3.37-3.25 (1H, m, CHNCH*H*), 2.85-2.73 (3H, m, $^{mi}N(CO)CH$, $^{mj}PhCH_2$), 2.72-2.61 (2H, m, $^{mi}PhCH_2$), 2.45-2.17 (2H, m, $^{mj}CH_2CH$), 2.17-1.97 (2H, m, $^{mi}CH_2CH$), 1.21-1.18 (6H, m, $^{mj}CH_3CHCH_3$) and 1.17-1.12 (6H, m, $^{mi}CH_3CHCH_3$); δ_C (100 MHz, $CDCl_3$) ^{mi}128.7 (Ph), ^{mi}128.6 (Ph), ^{mj}128.4 (Ph), ^{mj}128.3 (Ph), ^{mi}126.6 (*p*-Ph), ^{mj}126.1 (*p*-Ph), 57.3 (CH_2CH), 42.7, 40.8 ($CONHCH_2CH_2$), ^{mj}36.0 ($CHCH_3$), 34.6, 32.4 ($PhCH_2CH_2$), ^{mi}30.5 ($CHCH_3$) and 19.5, 19.2 (CH_3CHCH_3); *m*/*z* ($C_{16}H_{22}N_2NaO_2$ (M + Na$^+$) requires 297.1573) found 297.1575. This compound has not previously been reported.

3-Phenylethyl-4-pivaloylpiperazin-2-one (**4.24**)



Amine alkylation was carried out according to **General Method P** using **4.17** (10 mg, 0.05 mmol) and trimethylacetyl chloride (7 µL, 0.06 mmol). The residue was purified by silica column chromatography (eluent; Hexane:EtOAc (1:1) to EtOAc:MeOH (9:1)) to give a white crystalline solid (13 mg, 0.04 mmol, 89%); m.p.: 177-178 ^{o}C; υ_{max} (cm^{-1}) 3180 (NH), 3053, 2971, 2927 (CH_2, CH), 1662 (CON), 1621 (CONH), 1494 (Ph), 1456 (CH_2), 1348 (CH_3) 754, 702 (Ph); δ_H (400 MHz, $CDCl_3$) 7.31-7.26 (3H, m, CON*H* & *m*-Ph), 7.22-7.16 (3H, m, Ph), 5.16 (1H, t, *J* 6.5 C*H*CONH), 4.38-4.28 (1H, m, CONHCH$_2$C*H*H), 3.72-3.58 (2H, m, CONHC*H*$_2$CH$_2$), 3.51 (1H, ddd, *J* 14.5, 11.0, 4.0, CONHCH$_2$CH*H*), 2.84 (1H, ddd, *J* 13.5, 12.0, 5.0, PhC*H*HCH$_2$), 2.68 (1H, ddd, *J* 13.5, 11.5, 5.5, PhCH*H*CH$_2$), 2.37-2.25 (1H, m, PhCH$_2$C*H*H), 2.09-1.97 (1H, m, PhCH$_2$CH*H*) and 1.32 (9H, s, COC(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 176.1 (*C*ON), 170.8 (*C*ONH), 141.0 (*i*-Ph), 128.5 (Ph), 128.4 (Ph), 126.2 (*p*-Ph), 58.0 (*C*H), 45.9 (CONH*C*H$_2$CH$_2$), 43.8 (*C*(CH$_3$)$_3$), 39.0 (CONHCH$_2$*C*H$_2$), 34.1 (PhCH$_2$*C*H$_2$), 32.4 (Ph*C*H$_2$CH$_2$) and 28.2 (C(*C*H$_3$)$_3$); *m*/*z* ($C_{17}H_{24}N_2NaO_2$ (M + Na$^+$) requires 311.1730) found 311.1733. This compound has not previously been reported.

1,1,1-Trichloro-4-phenylbutan-2-one (**4.30**)

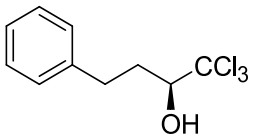


Oxidation was carried out according to **General Method N** using **4.12** (1.8 g, 7 mmol). The residues were purified by silica column chromatography (eluent; EtOAc:Hexane (1:9) to EtOAc) to give a colourless oil (1.4 g, 5.4 mmol, 54%); υ_{max} (cm^{-1}) 3028, 2927 (CH_2), 1749 ($COCCl_3$), 1604, 1496 (Ph), 1454 (CH_2), 806, 782 (CCl_3), 741, 697 (Ph); δ_H (400 MHz, $CDCl_3$) 7.35-7.30 (2H, m, *m*-Ph), 7.27-7.21 (3H, m, Ph), 3.32 (2H, t, *J* 7.5, C*H*$_2$CH$_2$CO) and 3.07 (2H, t, *J* 7.5, CH$_2$C*H*$_2$CO); δ_C (100 MHz, $CDCl_3$) 189.5 (*C*O), 139.5 (*i*-Ph), 128.6 (Ph), 128.3

(Ph), 126.5 (*p*-Ph), 96.2 (*C*Cl_3), 35.7 (CH_2*C*H_2CO) and 30.7 (*C*H_2CH_2CO). This compound is known but has previously only been reported with ^{1}H NMR data and IR data, which is consistent with that reported here.[237]

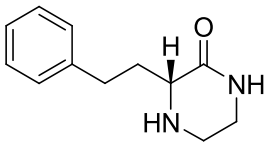
General Method Q: Asymmetric transfer hydrogenation reaction

(*S*)-1,1,1-Trichloro-4-phenylbutan-2-ol (**(*S*)-4.12**)



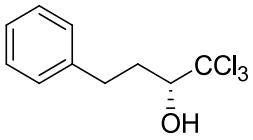
To 0.5 mL of a stock solution of (*p*-cymene)ruthenium(II) chloride dimer (3.1 mg, 0.005 mmol), ligand (1*S*,2*S*)-(+)-*N*-*p*-Tosyl-1,2-diphenylethylenediamine (3.7 mg, 0.01 mmol) and HCO_2H:NEt_3 complex (1 mL) was added **4.30** (252 mg, 1 mmol) and the resulting solution stirred under nitrogen at room temperature for 18 h. The reaction mixture was filtered through a plug of silica and washed with EtOAc:Petroleum Ether 40/60 ^oC (1:9). The organics were concentrated *in vacuo* to give a colourless oil (232 mg, 0.9 mmol, 91%); $[\alpha]_D^{27}$ (c = 1, MeOH) -36.1; υ_{max} (cm^{-1}) 3416, 3058 (OH), 2935, 2862 (CH_2, CH), 1600, 1494 (Ph), 1454 (CH_2), 1080, 1056 (COH), 801, 797 (CCl), 745, 699 (Ph); δ_H (400 MHz, $CDCl_3$) 7.27-7.20 (2H, m, *m*-Ph), 7.19-7.11 (3H, m, Ph), 3.94-3.86 (1H, m, C*H*OH), 2.93 (1H, ddd, *J* 14.0, 9.0, 5.0, C*H*HCH_2CH), 2.77 (1H, br s, OH), 2.70 (1H, dt, *J* 14.0, 8.5, CH*H*CH_2CH), 2.37-2.26 (1H, m, C*H*HCH) and 1.92 (1H, dddd, *J* 14.5, 10.0, 5.0, 1.0, CH*H*CH); δ_C (100 MHz, $CDCl_3$) 140.6 (*i*-Ph), 128.5 (Ph), 128.4 (Ph), 126.2 (*p*-Ph), 104.1 (*C*Cl_3), 81.9 (*C*HOH), 32.9 (CH_2*C*H_2CH) and 31.9 (*C*H_2CH_2CH). This data is consistent with that previously reported.[364]

(*R*)-3-Phenethylpiperazin-2-one (**(*R*)-4.17**)



Asymmetric heterocycle formation *via* the Jocic/Bargellini type reaction was carried out according to **General Method O** using **(*S*)-4.12** (91 mg, 0.36 mmol). The residue was purified by silica column chromatography (eluent; EtOAc to EtOAc:MeOH (8:2)) to give a white crystalline solid (14 mg, 0.07 mmol, 19%); m.p.: 145-146 ^{o}C; $[\alpha]_D^{25}$ (c = 0.7, MeOH) +18.1; υ_{max} (cm^{-1}) 3222 (NH), 3025 (CONH), 2926, 2860 (CH_2, CH), 1652 (CONH), 1492 (NH), 1452 (CH_2), 748, 699 (Ph); δ_H (400 MHz, $CDCl_3$) 7.35-7.28 (2H, m, *m*-Ph), 7.27-7.26 (2H, m, *o*-Ph), 7.24-7.18 (1H, m, *p*-Ph), 6.65 (1H, br s, CON*H*), 3.50-3.39 (2H, m C*H*NH & CONHC*H*H), 3.32 (1H, qd, *J* 7.0, 3.5 CONHCH*H*), 3.17 (1H, dt, *J* 13.0, 4.0, CHNHC*H*H), 2.99 (1H, ddd, *J* 13.0, 9.5, 4.0, CHNHCH*H*), 2.89-2.73 (2H, m, PhC*H*$_2$), 2.33 (1H, dddd, *J* 14.0, 10.5, 7.0, 4.0, PhCH$_2$C*H*H), 2.17-1.95 (2H, m, PhCH$_2$CH*H* & CHN*H*); δ_C (100 MHz, $CDCl_3$) 172.4 (*C*O), 141.5 (*i*-Ph), 128.4 (Ph), 128.3 (Ph), 125.9 (*p*-Ph), 58.3 (*C*H), 43.2 (CONH*C*H$_2$), 41.3 (CHNH*C*H$_2$), 33.5 (*C*H$_2$CHNH) and 32.1 (*C*H$_2$CH$_2$CH); *m*/*z* ($C_{12}H_{17}N_2O$ (M + H$^+$) requires 205.1335) found 205.1335. This compound has not previously been reported.

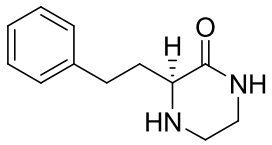
(*R*)-1,1,1-Trichloro-4-phenylbutan-2-ol (**(*R*)-4.12**)



Asymmetric transfer hydrogenation was carried out according to **General Method Q** using **4.30** (252 mg, 1 mmol) and (1*R*,2*R*)-(−)-*N*-*p*-Tosyl-1,2-diphenylethylenediamine in place of (1*S*,2*S*)-(+)-*N*-*p*-Tosyl-1,2-diphenylethylenediamine to give a colourless oil (244 mg, 0.96 mmol, 96%);

$[\alpha]_D^{27}$ (c = 1, MeOH) +38.7; υ_{max} (cm^{-1}) 3321 (OH), 2941, 2888 (CH_2, CH), 1602, 1499 (Ph), 1454 (CH_2), 1078, 1056 (COH), 800, 795 (CCl), 747, 700 (Ph); δ_H (400 MHz, $CDCl_3$) 7.28-7.21 (2H, m, *m*-Ph), 7.19-7.12 (3H, m, Ph), 3.91 (1H, ddd, *J* 10.0, 5.5, 2.0 C*H*OH), 2.93 (1H, ddd, *J* 14.0, 9.0, 5.0, C*H*HCH$_2$CH), 2.76-2.65 (2H, m, CH*H*CH$_2$CHO*H*), 2.37-2.26 (1H, m, C*H*HCH) and 1.97-1.86 (1H, m, CH*H*CH); δ_C (100 MHz, $CDCl_3$) 140.7 (*i*-Ph), 128.6 (Ph), 128.5 (Ph), 126.3 (*p*-Ph), 104.1 (*C*Cl$_3$), 82.0 (*C*HOH), 32.9 (CH$_2$*C*H$_2$CH) and 31.9 (*C*H$_2$CH$_2$CH); This data is consistent with that previously reported.[237,365]

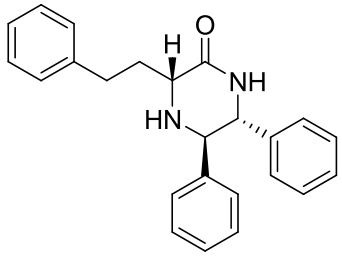
(*S*)-3-Phenethylpiperazin-2-one (**(*S*)-4.17**)



Asymmetric heterocycle formation *via* the Jocic/Bargellini type reaction was carried out according to **General Method O** using **(*R*)-4.12** (50 mg, 0.2 mmol). The residue was purified by silica column chromatography (eluent; EtOAc:Hexane (1:1) to EtOAc:MeOH (8:2)) to give a white crystalline solid (12 mg, 0.06 mmol, 30%); m.p.: 133-134 ^oC; $[\alpha]_D^{25}$ (c = 0.24, MeOH) -30.8; υ_{max} (cm^{-1}) 3201 (NH), 3025 (CONH), 2922, 2857 (CH_2, CH), 1653 (CONH), 1493 (NH), 1453 (CH_2), 749, 699 (Ph); δ_H (400 MHz, $CDCl_3$) 7.30-7.25 (2H, m, *m*-Ph), 7.24-7.20 (2H, m, *o*-Ph), 7.18 (1H, m, *p*-Ph), 6.73 (1H, br s, CON*H*), 3.43 (1H, dd, *J* 8.5, 3.5, C*H*NH), 3.40 (1H, ddd, *J* 9.5, 4.5, 1.0, CONHC*H*H), 3.31-3.24 (1H, m, CONHCH*H*), 3.13 (1H, dtd, *J* 13.5, 4.0, 0.5, CHNHC*H*H), 2.95 (1H, ddd, *J* 13.5, 9.5, 4.0, CHNHCH*H*), 2.85-2.69 (2H, m, C*H*$_2$CH$_2$CH), 2.29 (1H, dddd, *J* 14.0, 10.5, 7.0, 4.0, C*H*HCHNH), 2.05-1.86 (2H, m, CH*H*CHNH & CHN*H*); δ_C (100 MHz, $CDCl_3$) 172.4 (*C*O), 141.5 (*i*-Ph), 128.4 (Ph), 128.3 (Ph), 125.9 (*p*-Ph), 58.3 (*C*H), 43.2 (CONH*C*H$_2$), 41.3 (CHNH*C*H$_2$), 33.6

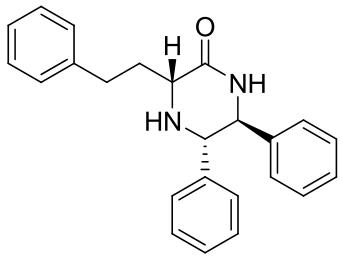
(*C*H_2CHNH) and 32.1 (*C*H_2CH_2CH); *m*/*z* ($C_{12}H_{17}N_2O$ (M + H^+) requires 205.1335) found 205.1335. This compound has not previously been reported.

(3*R*,5*R*,6*R*)-3-Phenylethyl-5,6-diphenylpiperazin-2-one (**4.41**)



Asymmetric heterocycle formation was carried out according to **General Method O** using **(*S*)-4.12** (52 mg, 0.2 mmol) and (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (42 mg, 0.2 mmol). The residue was purified by silica column chromatography (eluent; Hexane:EtOAc (1:1) to EtOAc) to give a white crystalline solid (72 mg, 0.2 mmol, 98%); m.p.: 138-139 ^oC; $[\alpha]_D^{27}$ (c = 0.6, MeOH) +109.2; υ_{max} (cm^{-1}) 3167, 3060, 3030 (NH, CONH), 2923, 2880 (CH_2), 1670 (CONH), 1603 (Ph), 1491 (NH), 1453, 1402 (CH_2), 768, 751, 695 (Ph); δ_H (400 MHz, $CDCl_3$) 7.39-7.24 (11H, m, Ph), 7.22-7.17 (2H, m, Ph), 7.11-7.06 (2H, m, Ph), 6.21 (1H, br s, CON*H*), 4.69 (1H, d, *J* 8.5, CONHC*H*Ph), 4.11 (1H, d, *J* 8.5, CHNHC*H*Ph), 3.80 (1H, dd, *J* 9.5, 4.5, CH_2CH), 2.96-2.82 (2H, m, CH_2CH_2CH), 2.49 (1H, dddd, *J* 14.0, 9.5, 7.0, 4.5, CH_2C*H*HCH), 2.31 (1H, dtd, *J* 14.0, 9.5, 6.0, CH_2CH*H*CH) and 2.24 (1H, br s, CH_2CHN*H*); δ_C (100 MHz, $CDCl_3$) 172.6 (*C*O), 141.0 (CONHCH(*i-Ph*)), 138.8 (CH_2(*i-Ph*)), 138.7 (CHNHCH(*i-Ph*)), 128.5 (Ph), 128.42 (Ph), 128.40 (Ph), 128.34 (Ph), 128.26 (Ph), 128.1 (Ph), 127.7 (Ph), 127.1 (Ph), 126.0 (CH_2(*p-Ph*)), 64.3 (CHNH*C*HPh), 60.0 (CONH*C*HPh), 57.2 (CH_2*C*H), 33.6 (*C*H_2CHNH) and 32.6 (*C*H_2CH_2CH); *m*/*z* ($C_{24}H_{25}N_2O$ (M + H^+) requires 357.1961) found 357.1964. This compound has not previously been reported.

(3*R*,5*S*,6*S*)-3-Phenylethyl-5,6-diphenylpiperazin-2-one (**4.42**)



Asymmetric heterocycle formation was carried out according to **General Method O** using (*S*)-1,1,1-trichloro-4-phenylbutan-2-ol (58 mg, 0.2 mmol) and (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine (42 mg, 0.2 mmol). The residue was purified by silica column chromatography (eluent; Hexane:EtOAc (1:1) to EtOAc) to give a white crystalline solid (78 mg, 0.2 mmol, 96%); m.p.: 127-128 ^{o}C; $[\alpha]_D^{26}$ (c = 0.44, MeOH) -67.8; υ_{max} (cm^{-1}) 3169, 3060, 3028 (NH, CONH), 2923, 2878 (CH_2), 1670 (CONH), 1605 (Ph), 1490 (NH), 1453, 1408 (CH_2), 769, 751, 696 (Ph); δ_H (400 MHz, $CDCl_3$) 7.33-7.16 (11H, m, Ph), 7.11-7.05 (2H, m, Ph), 7.00-6.95 (2H, m, Ph), 5.97 (1H, br s, CON*H*), 4.54 (1H, d, *J* 9.5, CONHC*H*Ph), 3.86 (1H, d, *J* 9.5, CHNHC*H*Ph), 3.81 (1H, dd, *J* 7.0, 4.0, CH_2C*H*), 2.93-2.78 (2H, m, C*H*$_2$CH$_2$CH), 2.37 (1H, dddd, *J* 14.0, 10.5, 7.0, 4.0, CH_2C*H*HCH), 2.26-2.15 (1H, m, CH_2C*H*HCH) and 2.06 (1H, br s, CH_2CHN*H*); δ_C (100 MHz, $CDCl_3$) 171.6 (*C*O), 141.6 (CONHCH(*i-Ph*)), 138.8 (CH_2(*i-Ph*)), 138.3 (CHNHCH(*i-Ph*)), 128.5 (Ph), 128.4 (Ph), 128.34 (Ph), 128.31 (Ph), 128.24 (Ph), 128.19 (Ph), 127.8 (Ph), 127.4 (Ph), 125.9 (CH_2(*p-Ph*)), 66.3 (CHNH*C*HPh), 65.1 (CONH*C*HPh), 59.1 (CH_2*C*H), 33.9 (*C*H_2CHNH) and 31.8 (*C*H_2CH_2CH); *m*/*z* ($C_{24}H_{25}N_2O$ (M + H$^+$) requires 357.1961) found 357.1964. This compound has not previously been reported.

5.5 References

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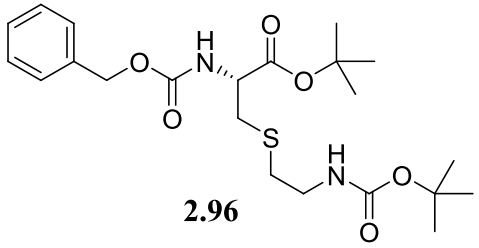
APPENDIX I - Representative ^{1}H and ^{13}C NMR Traces

Index



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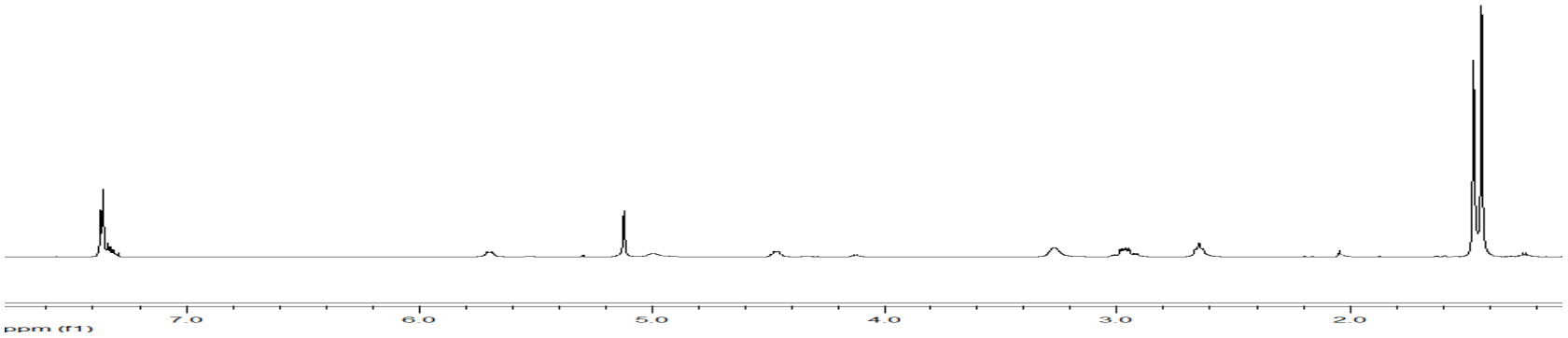

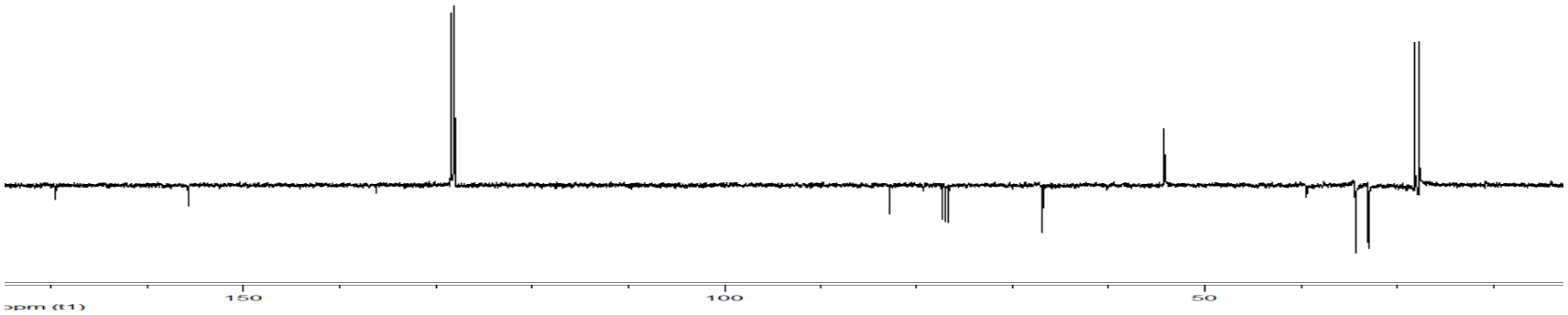

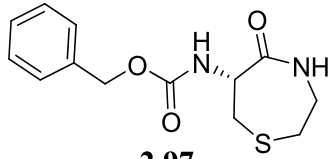

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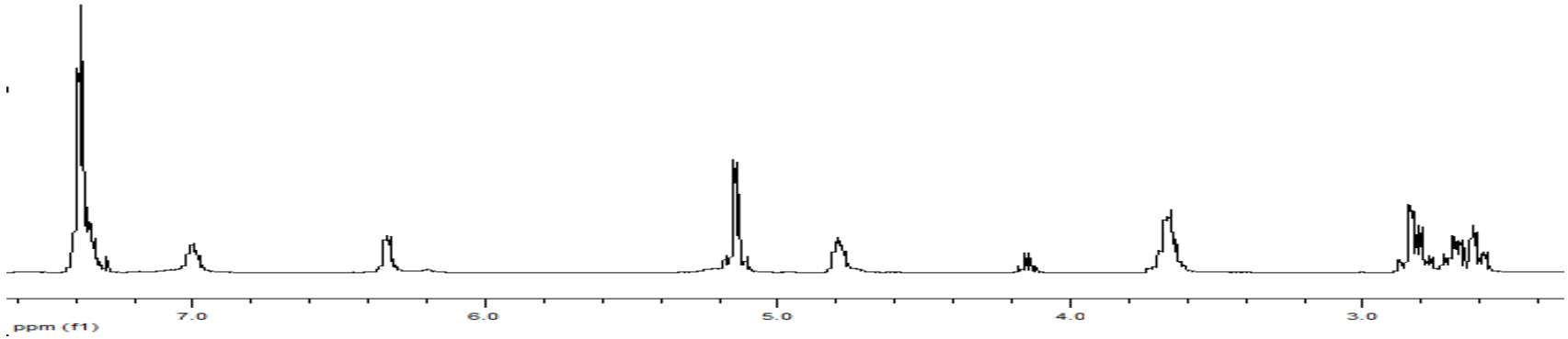

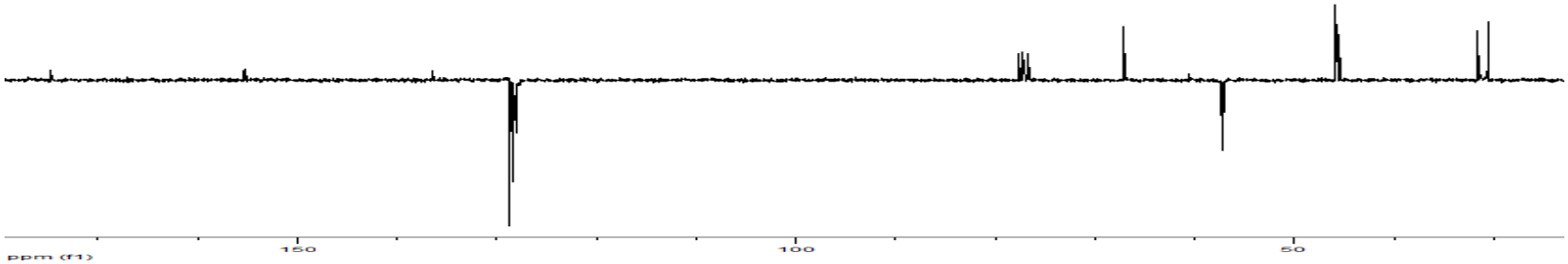

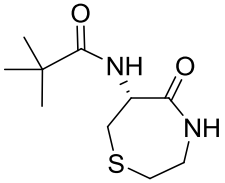

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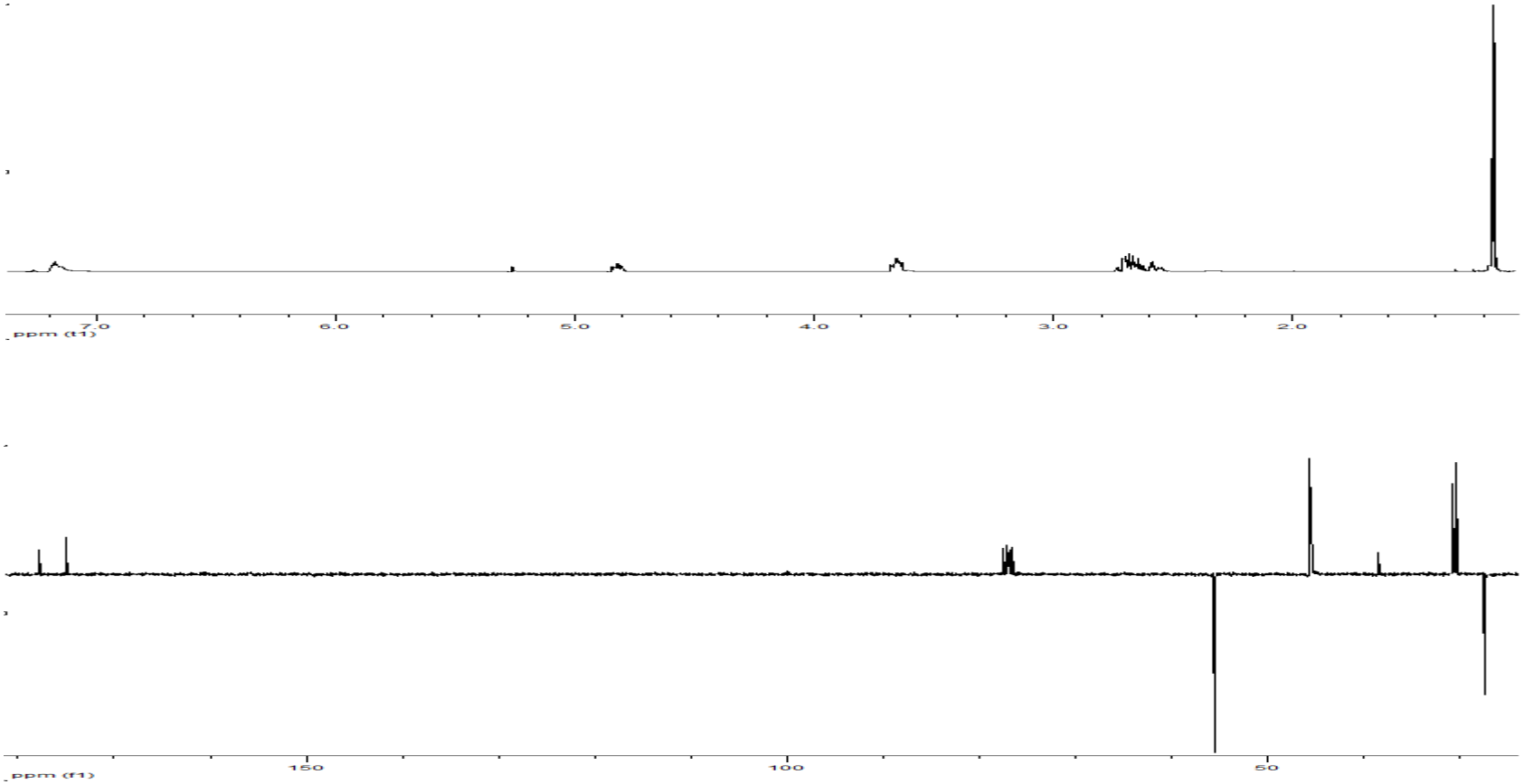

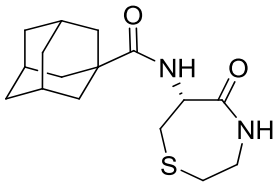

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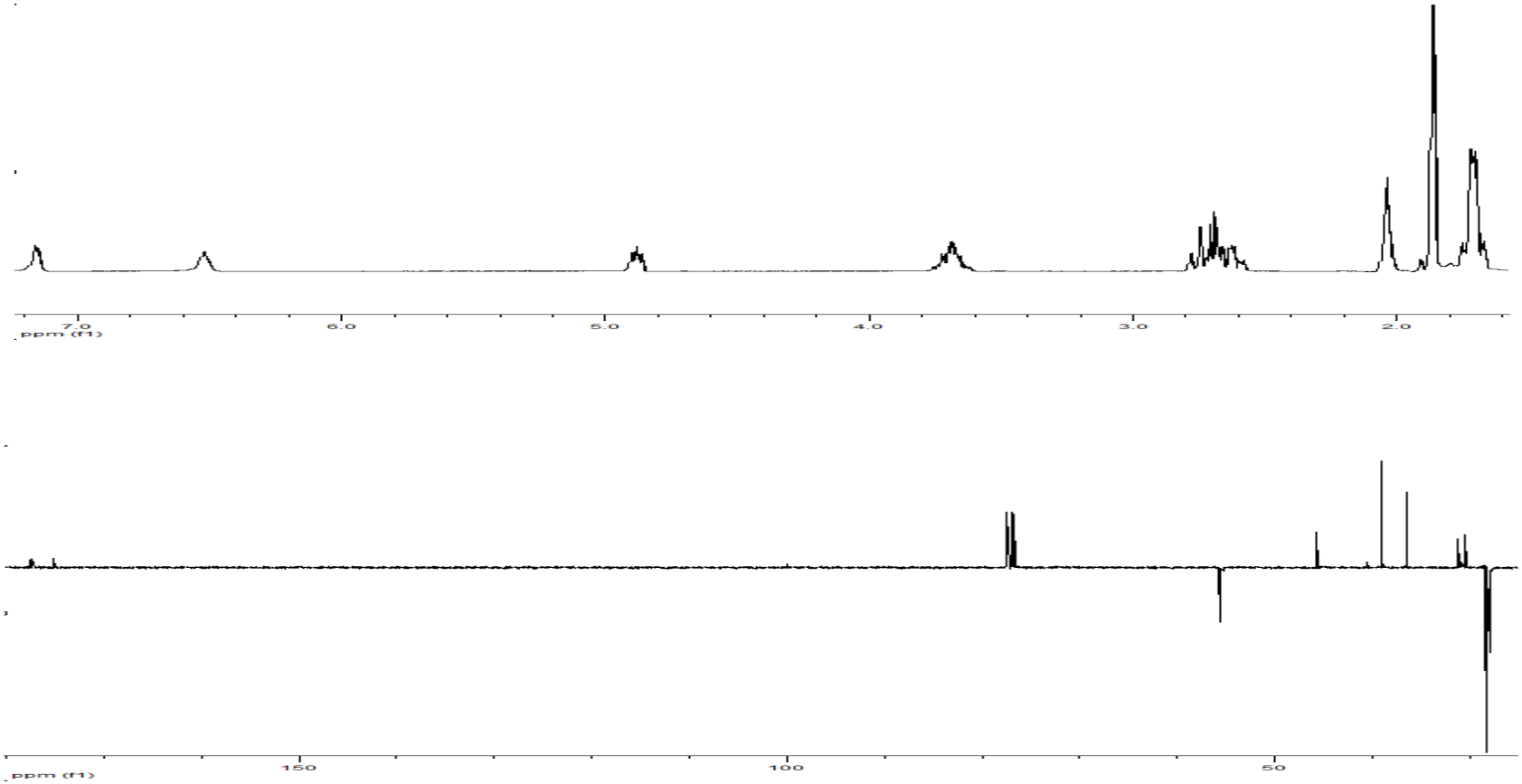

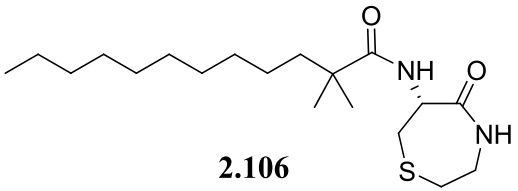

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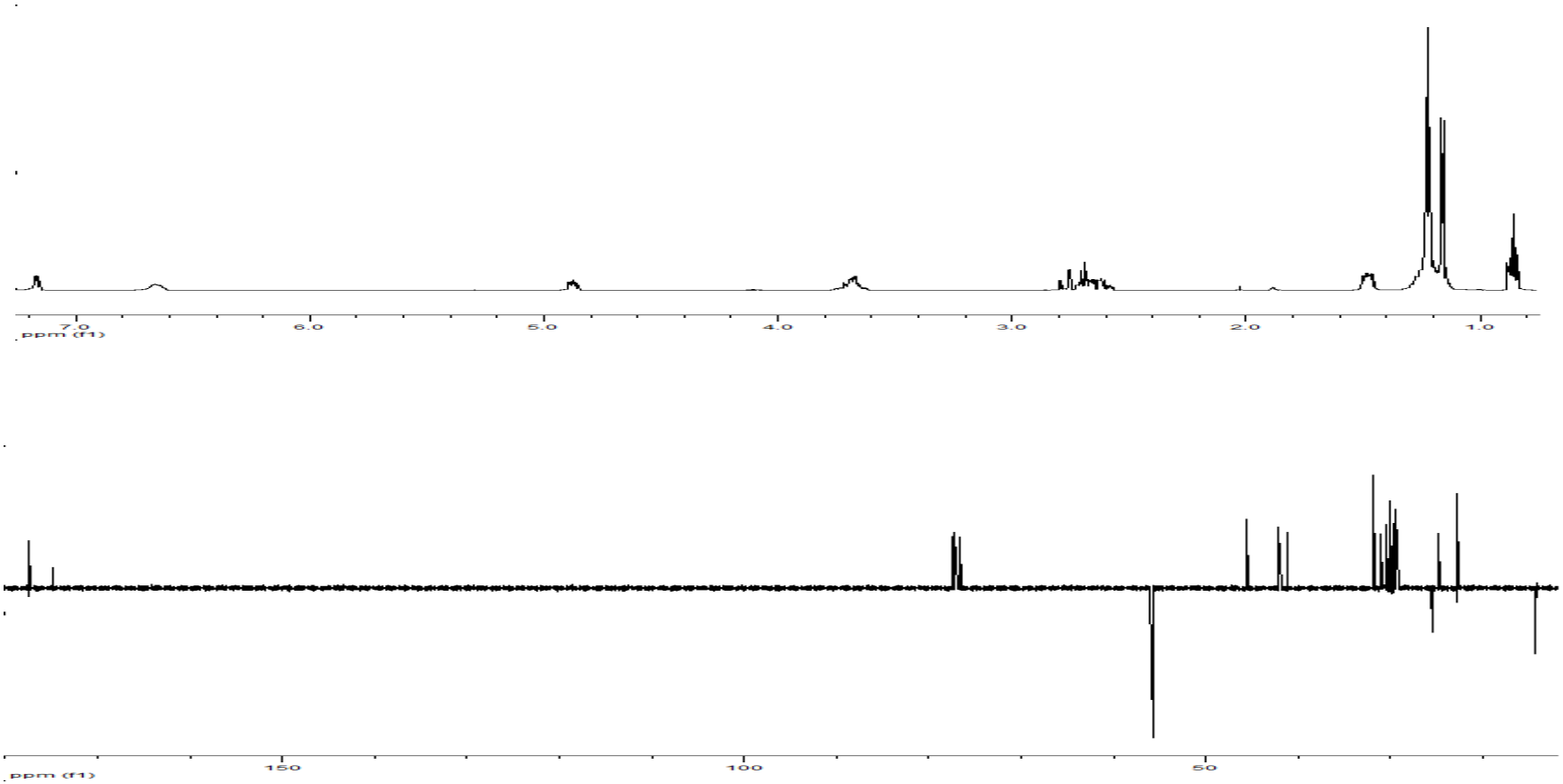

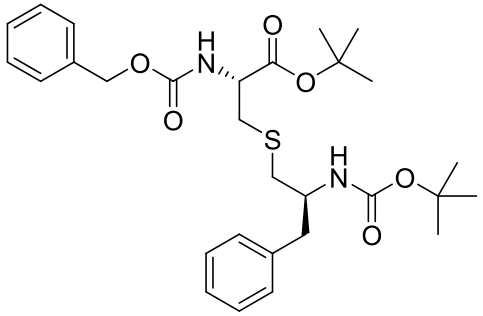

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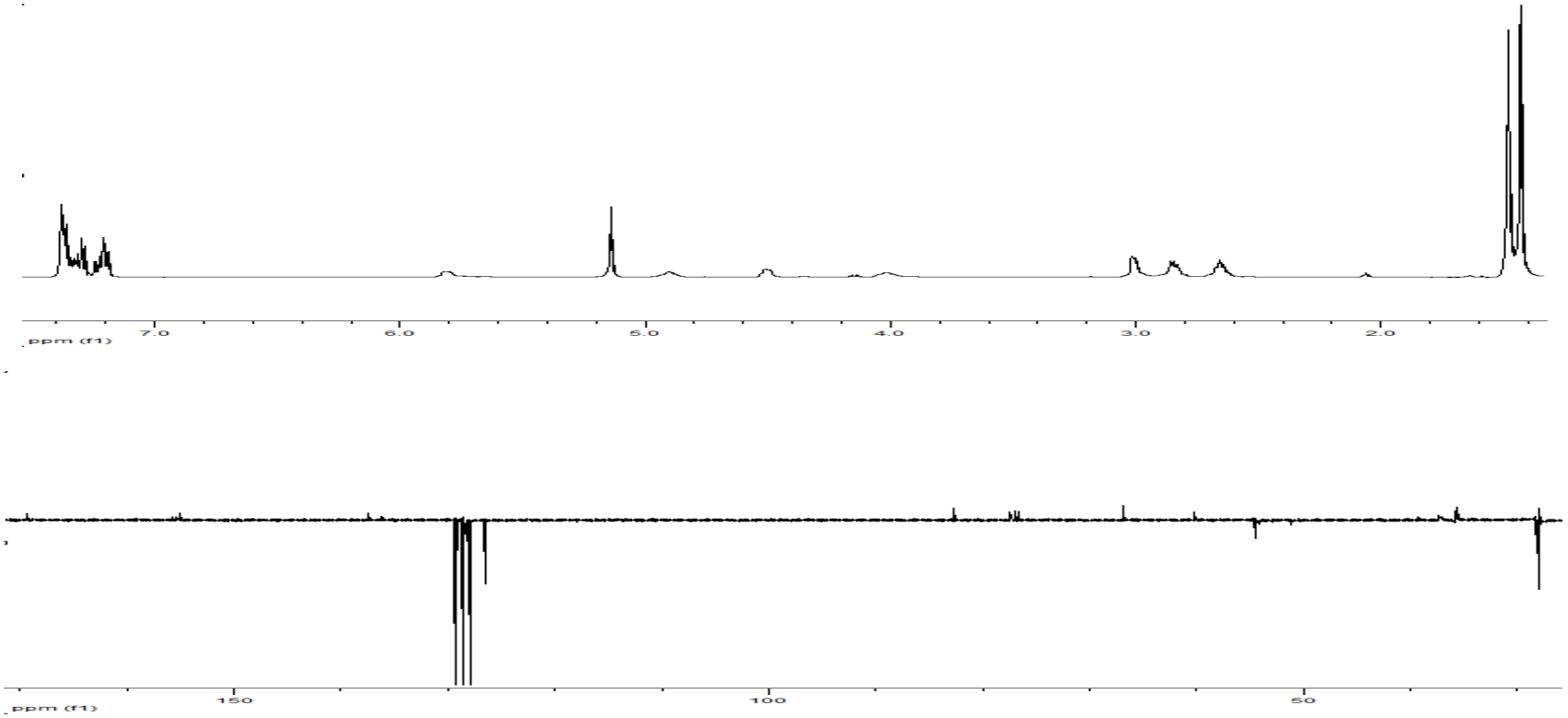

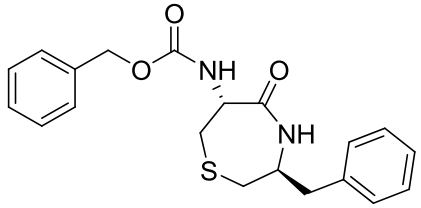

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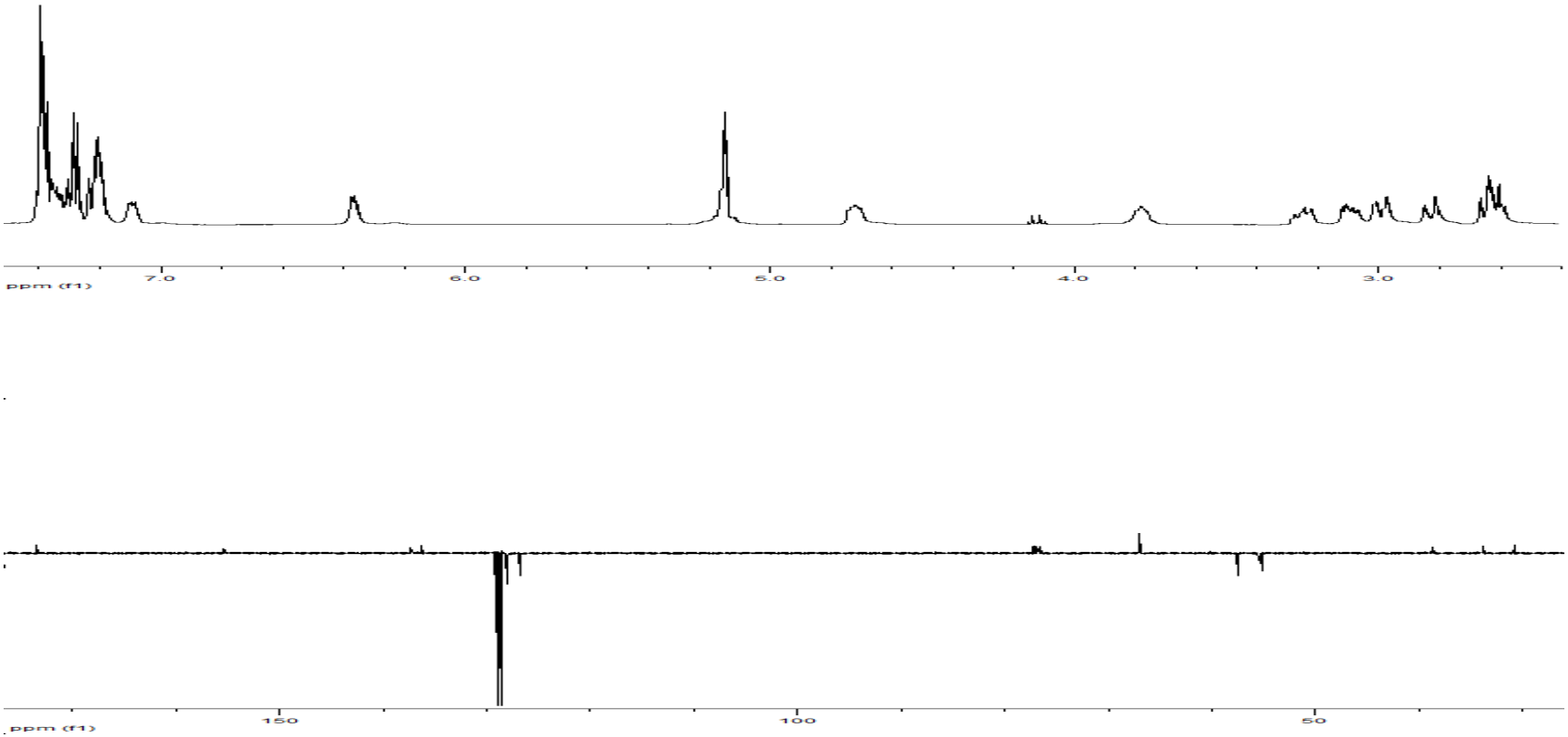

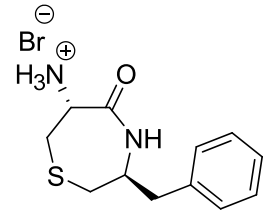

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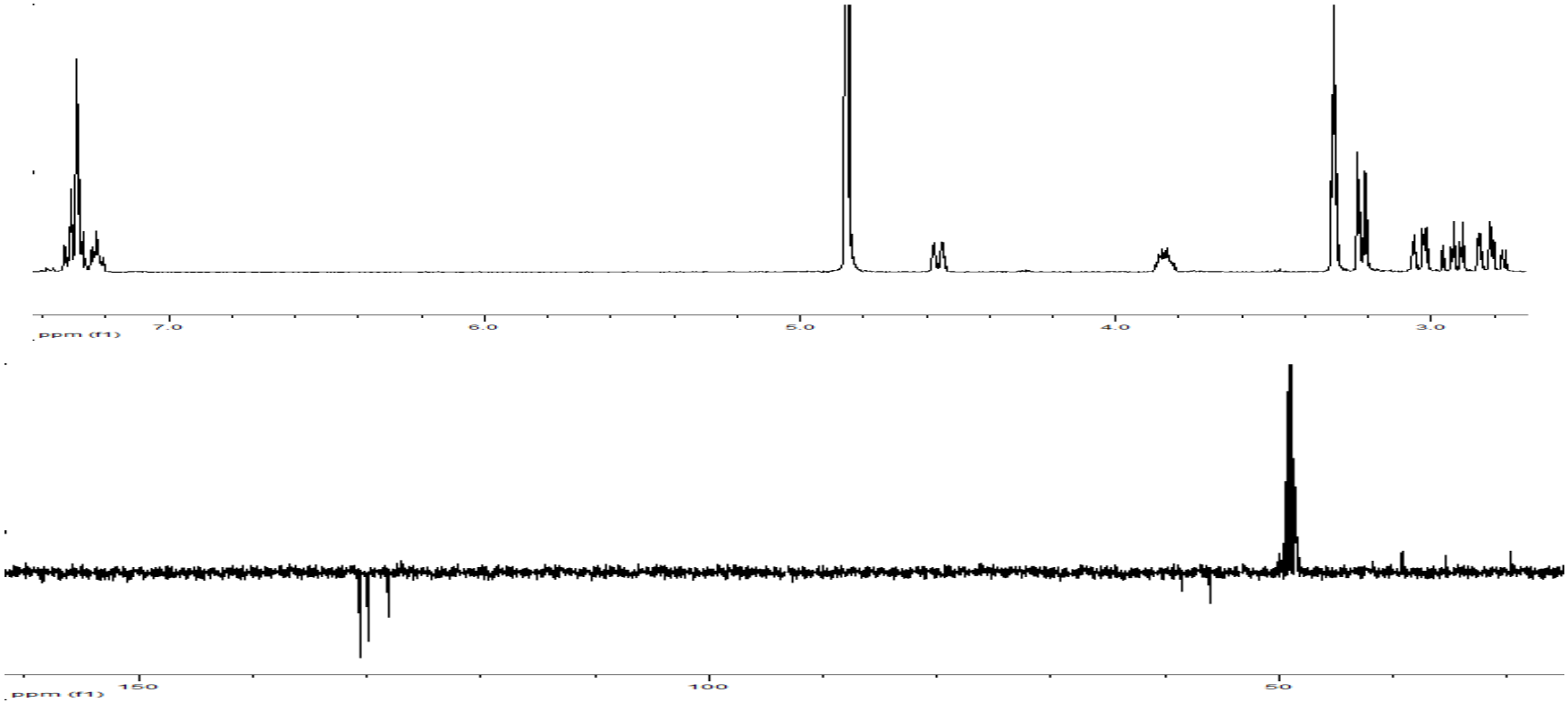

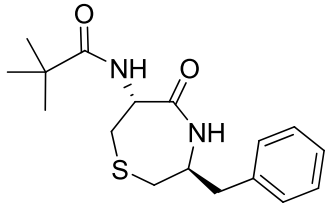

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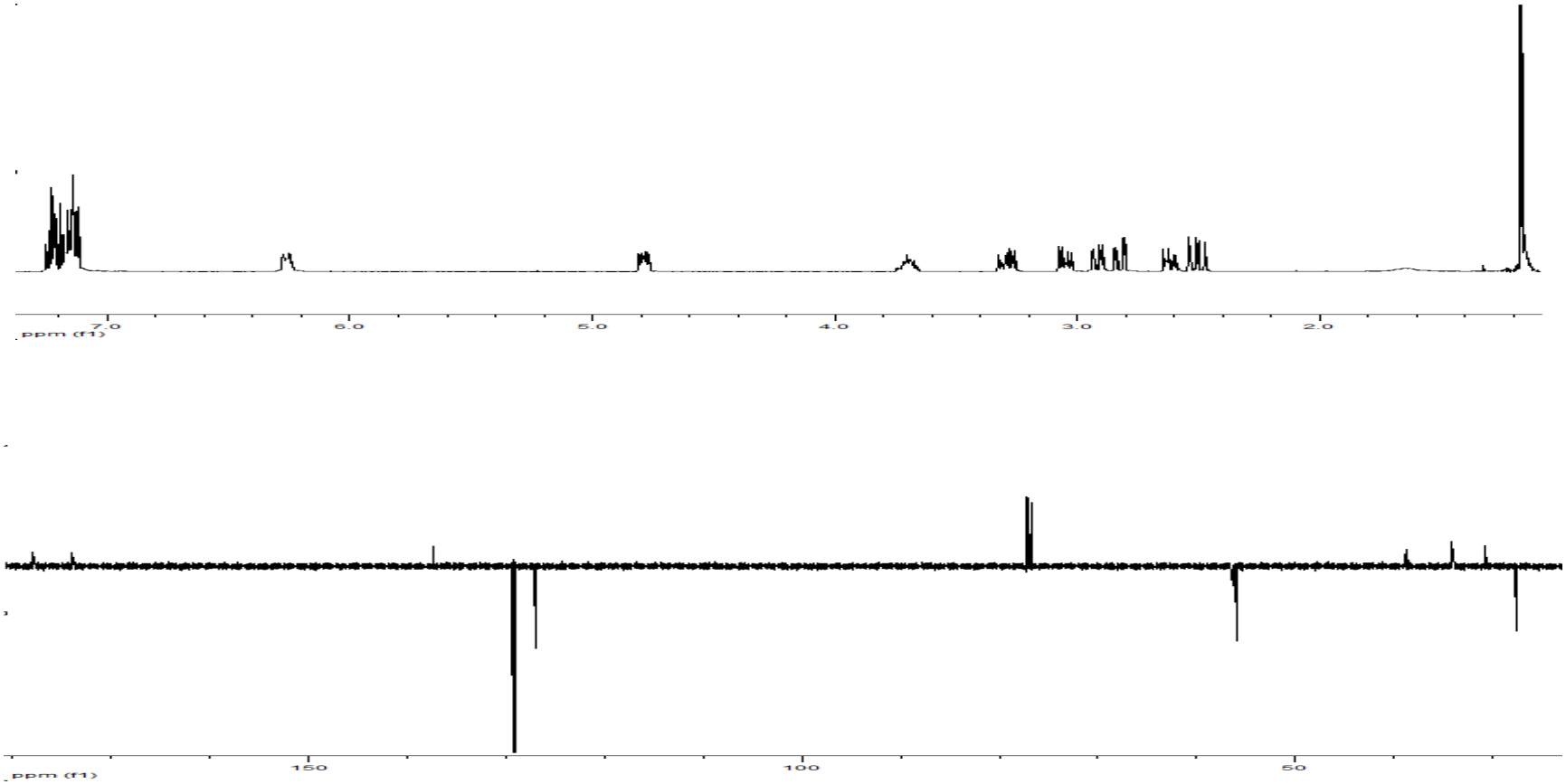

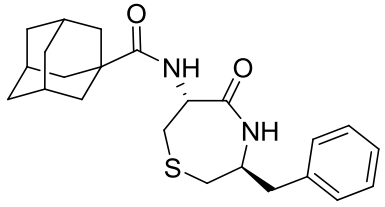

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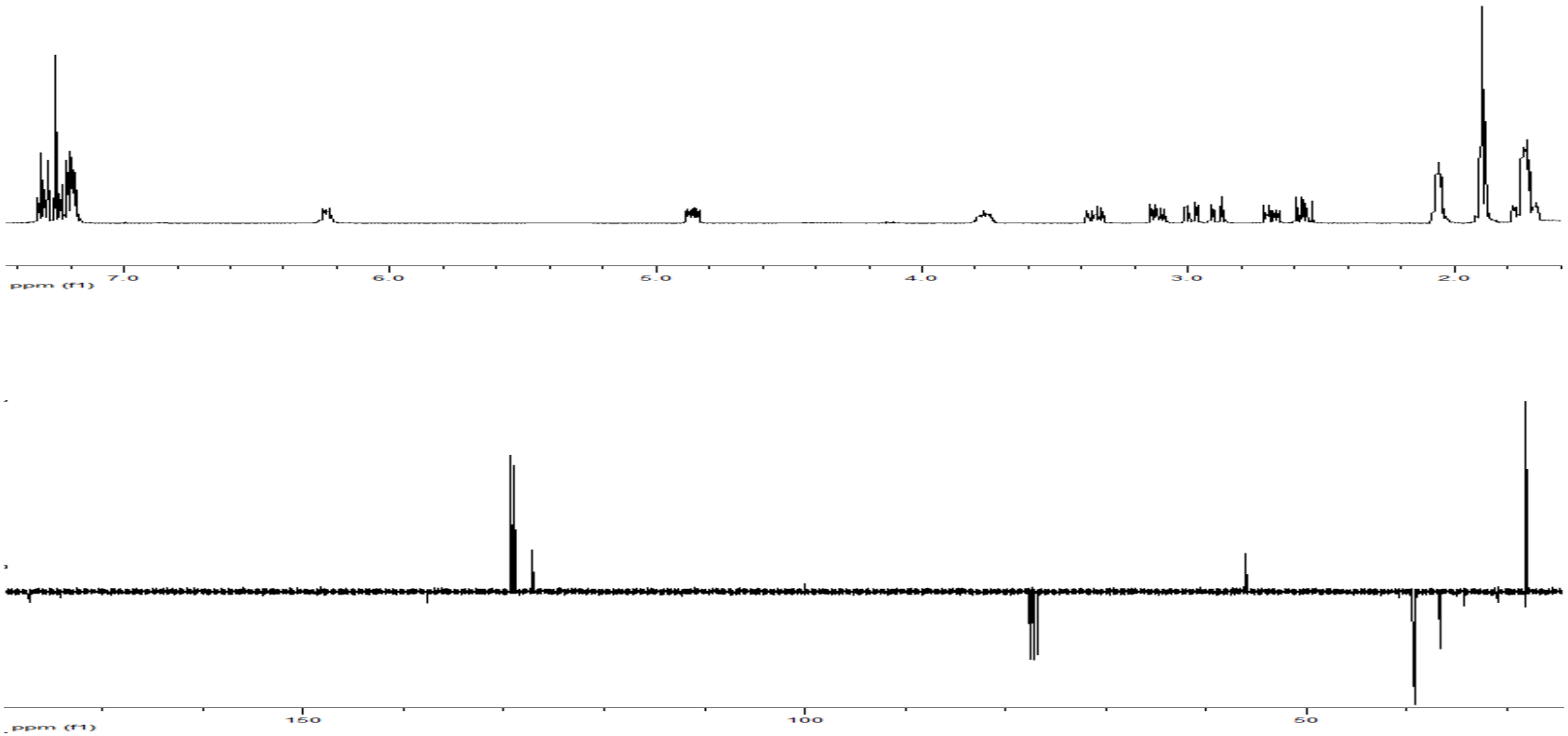

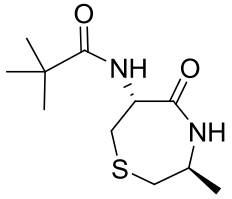

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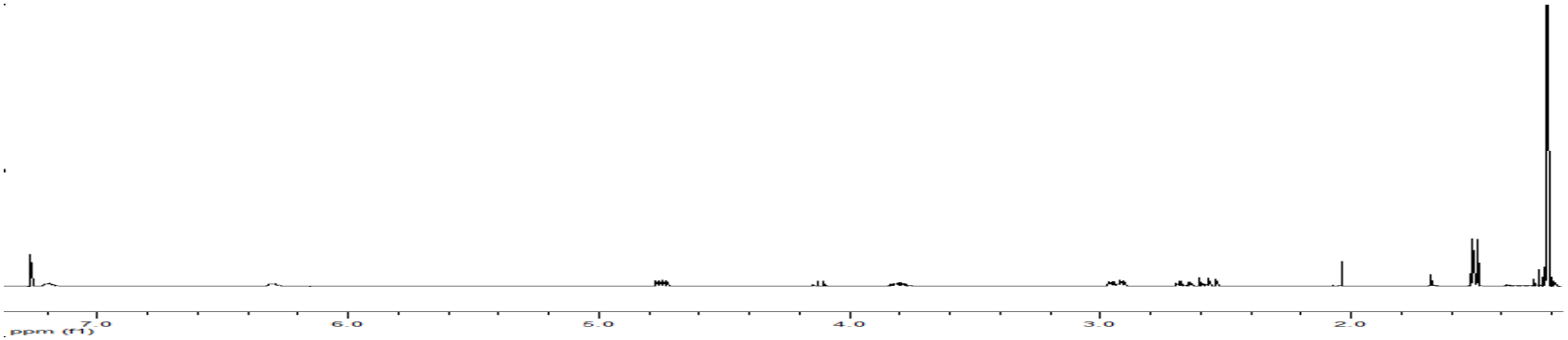
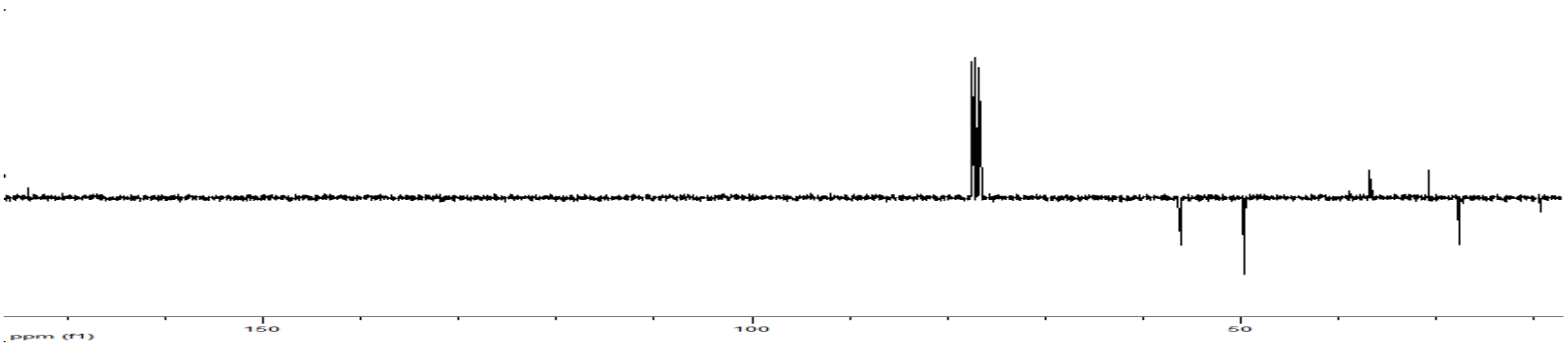
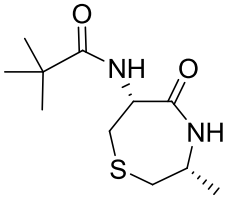
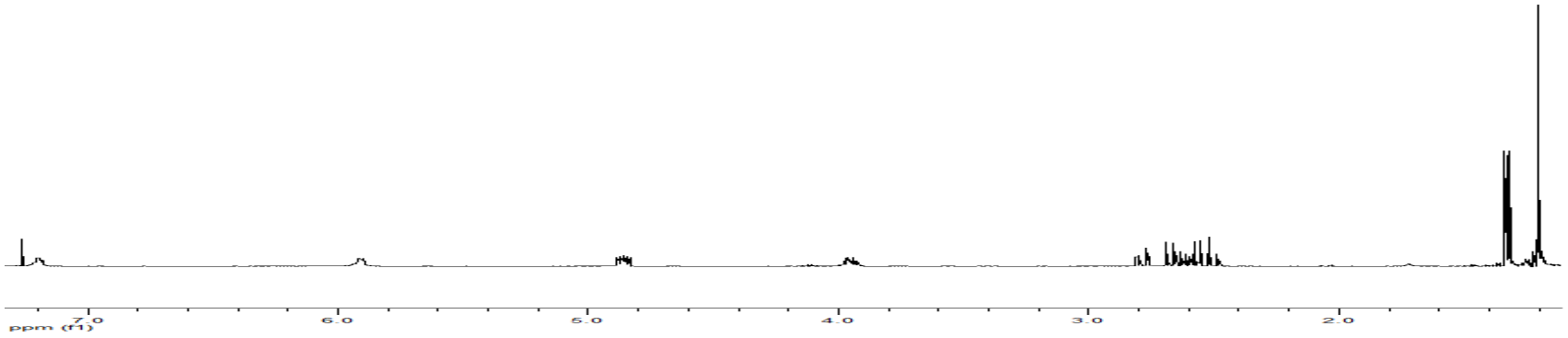
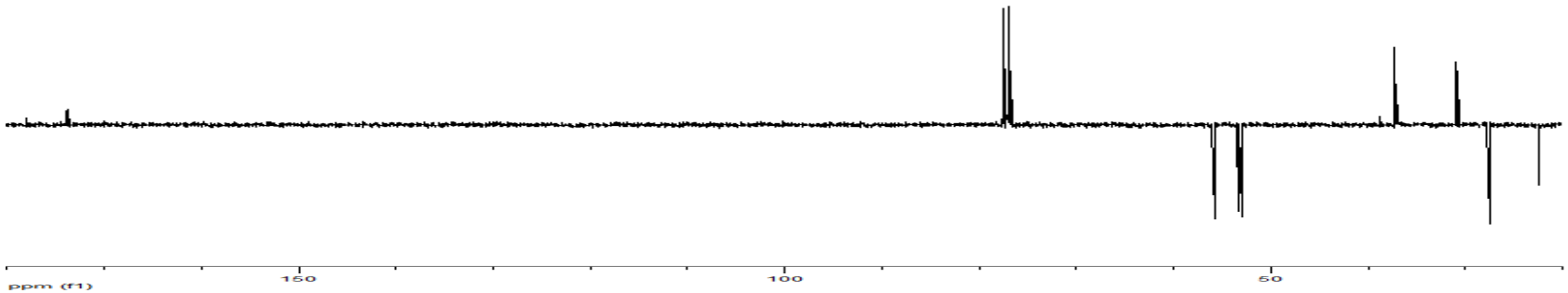


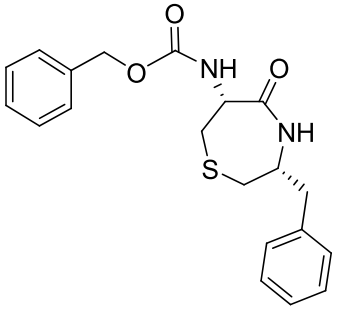




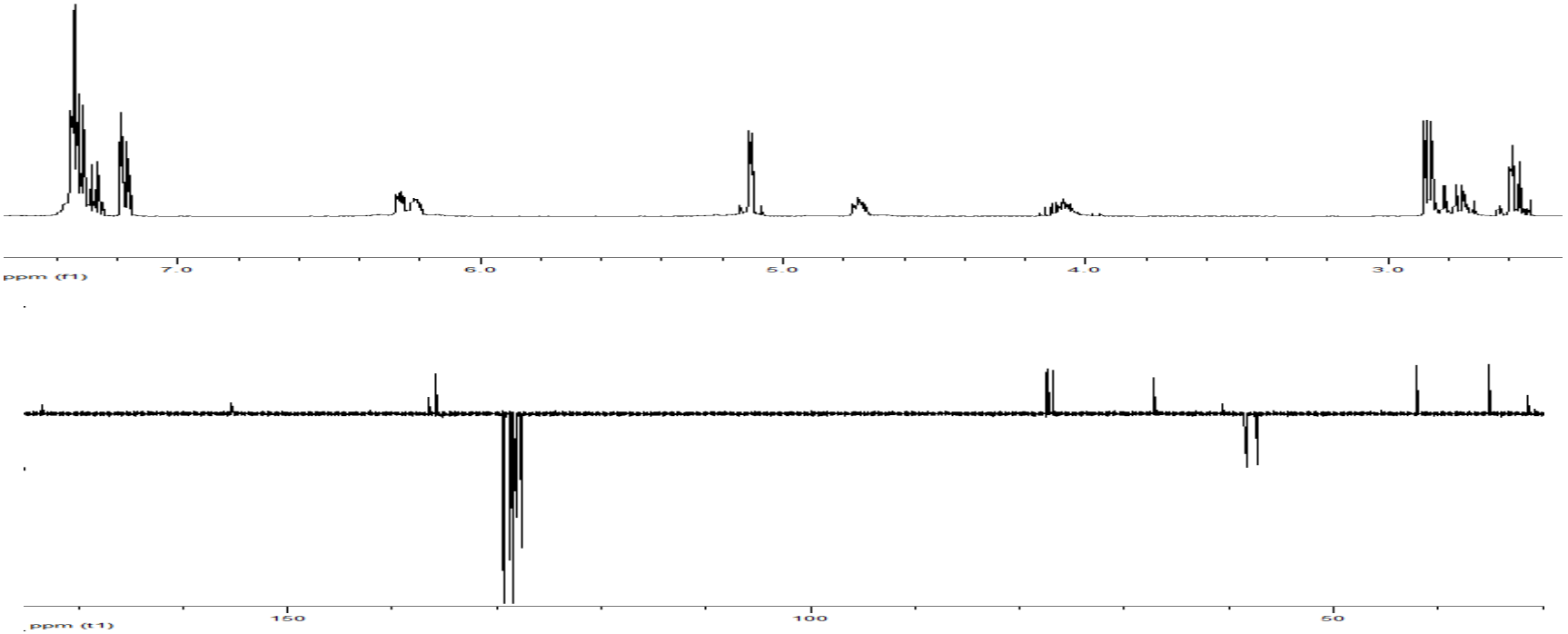
(3*R*,6*R*)-2.111

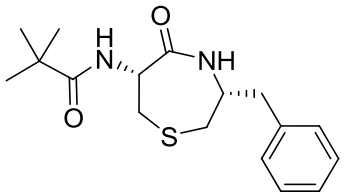




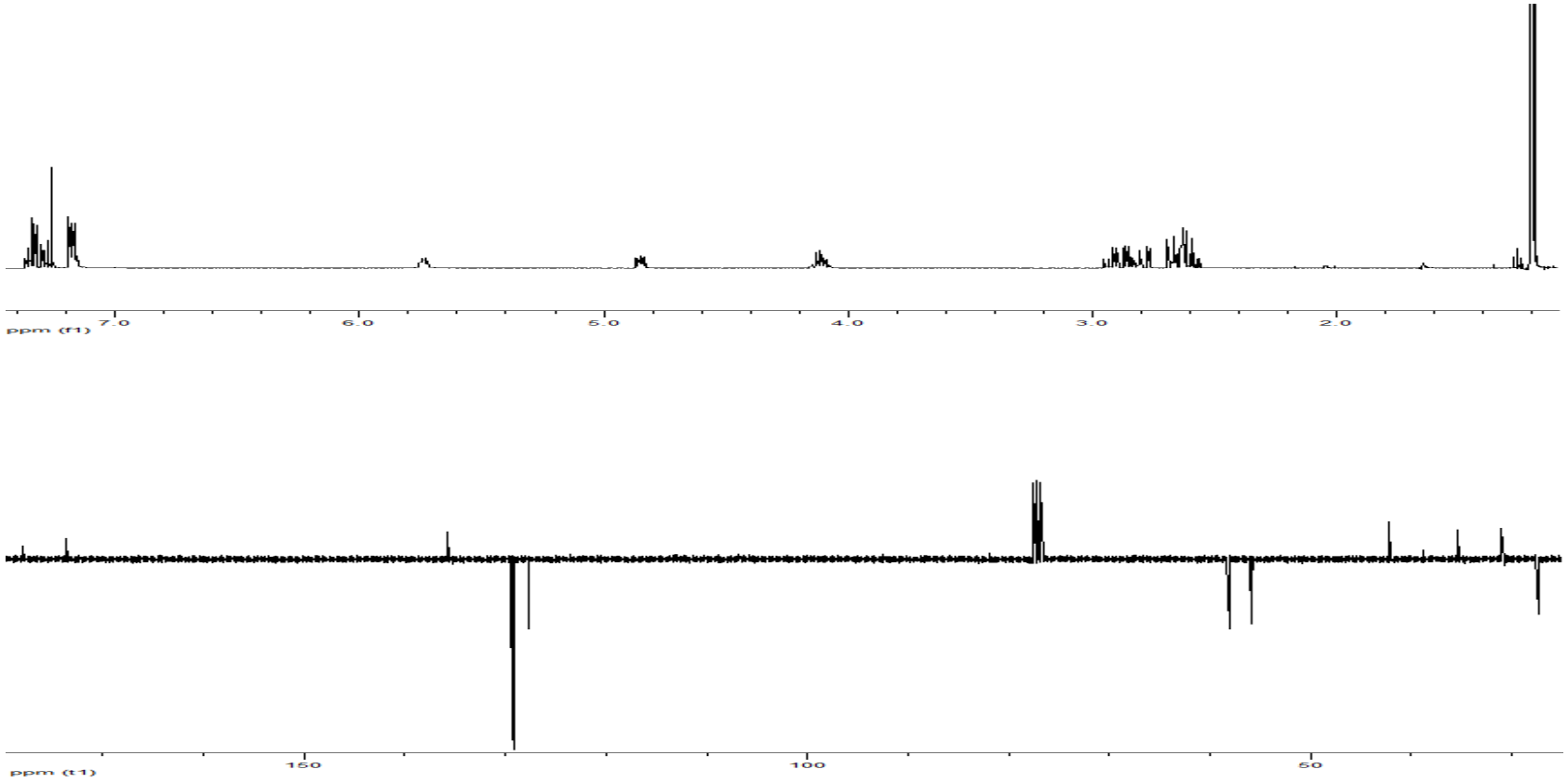


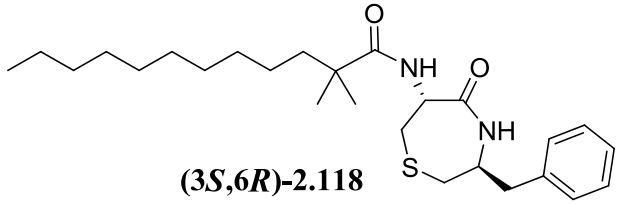
(3*R*,6*R*)-2.114



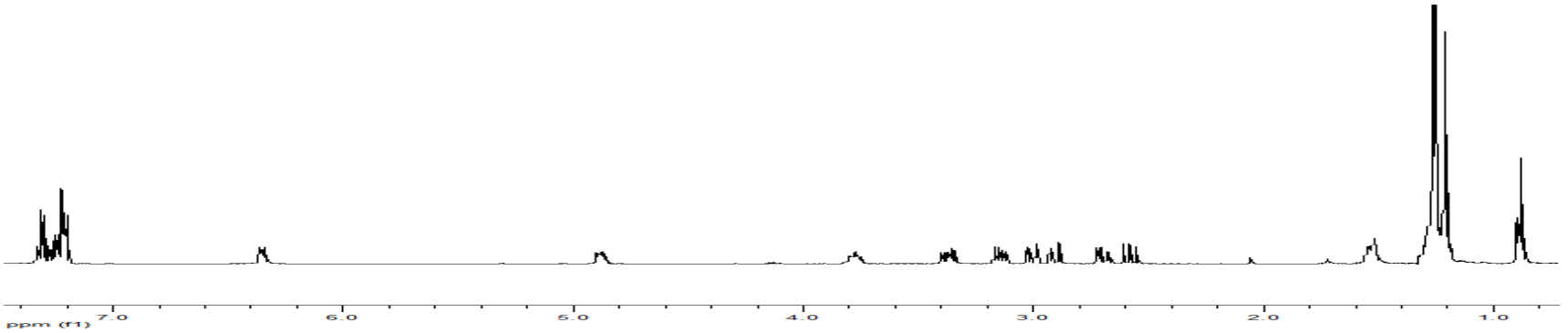


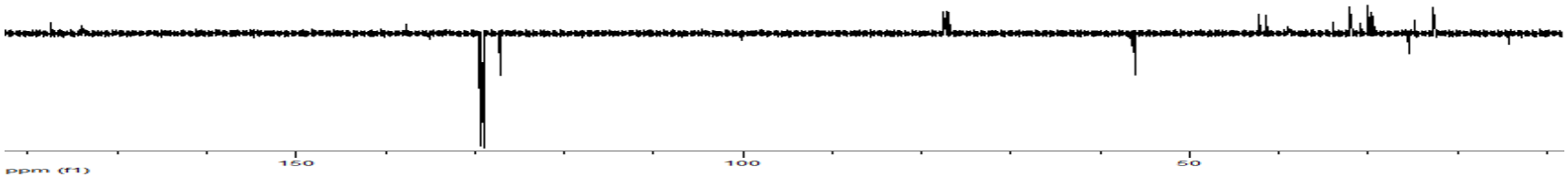
(3*R*,6*R*)-2.116

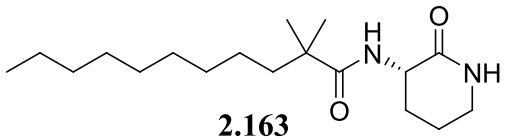




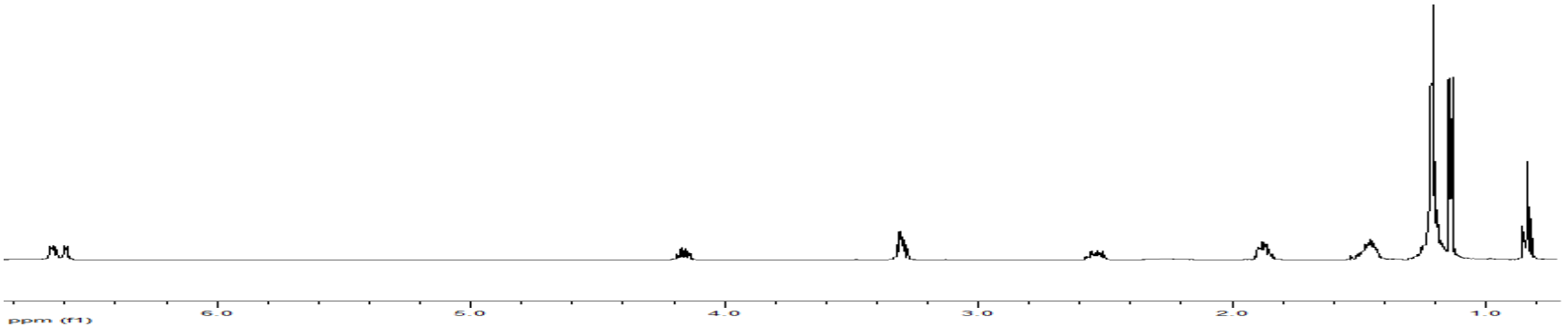
(3*S*,6*R*)-2.118

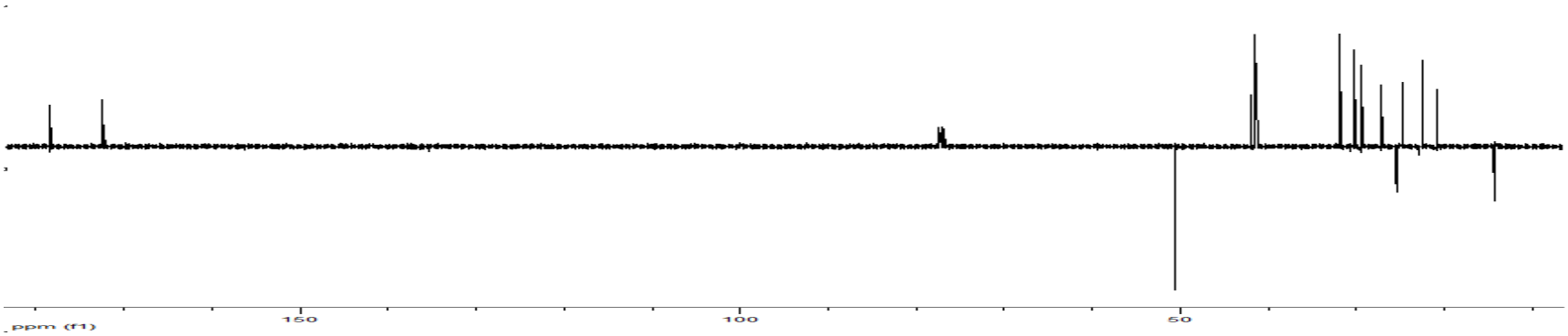


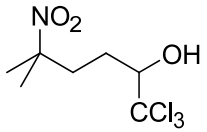




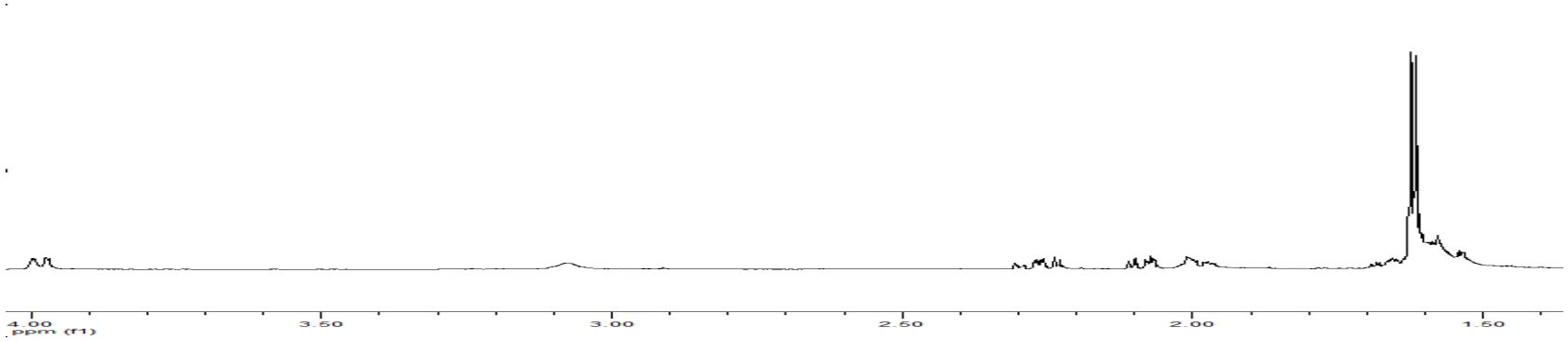
2.163






NO2
OH
CCl3

3.52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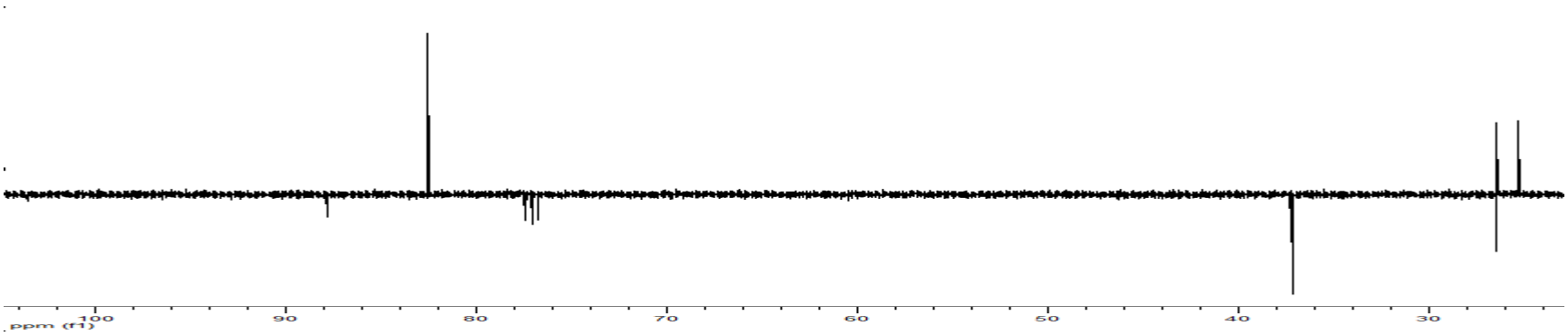
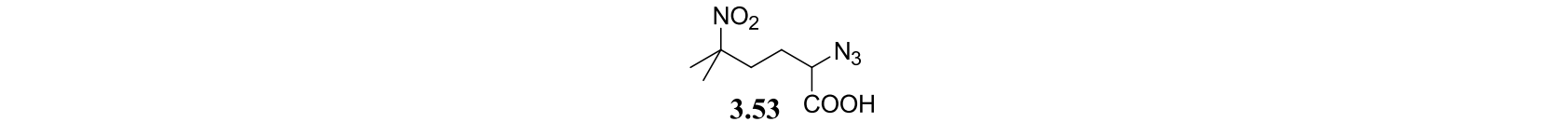
3.00
2.50
2.00
1.50
ppm (f1)


100
90
80
70
60
50
40
30
ppm (f1)



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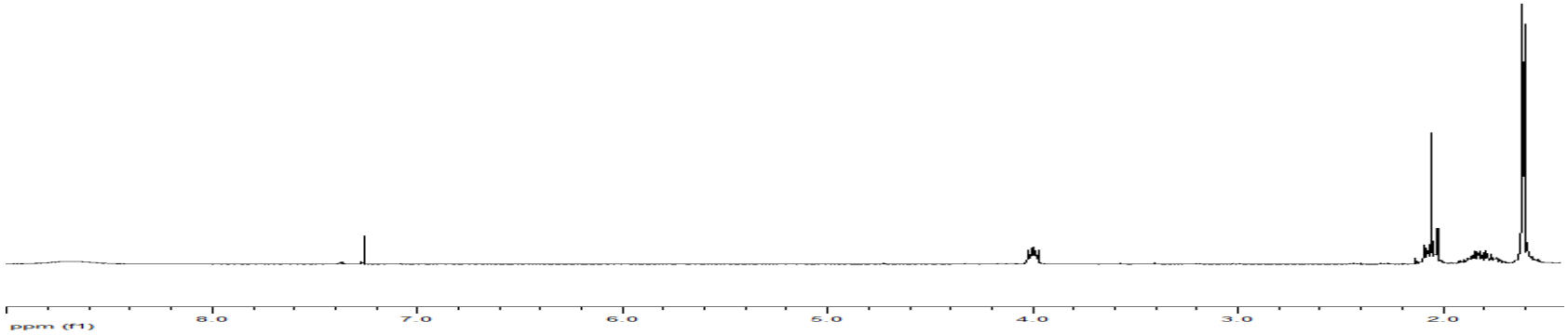
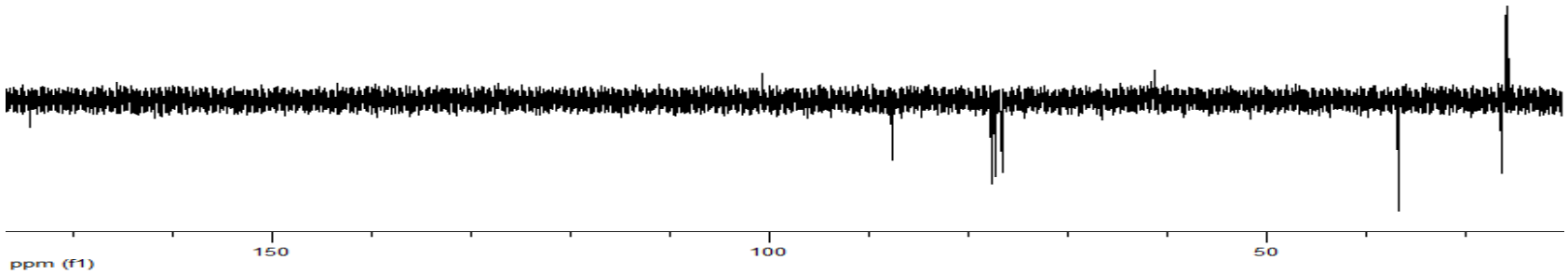
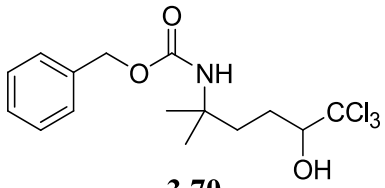
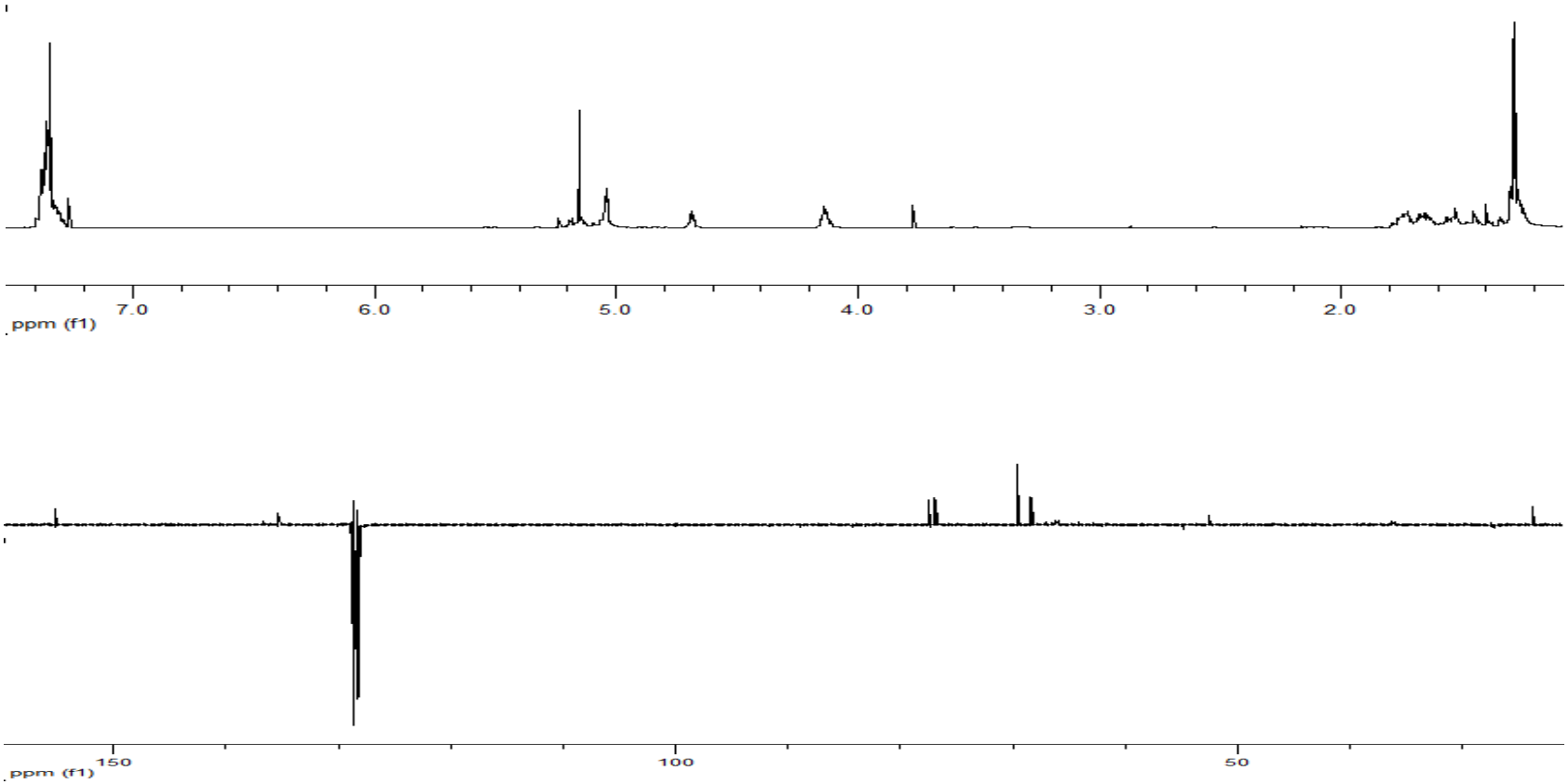
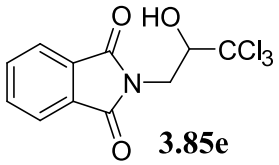




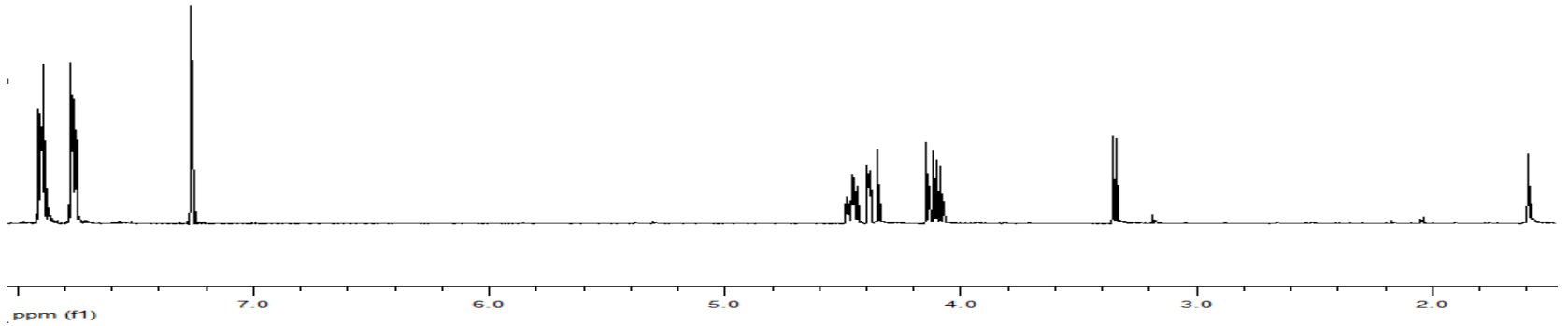


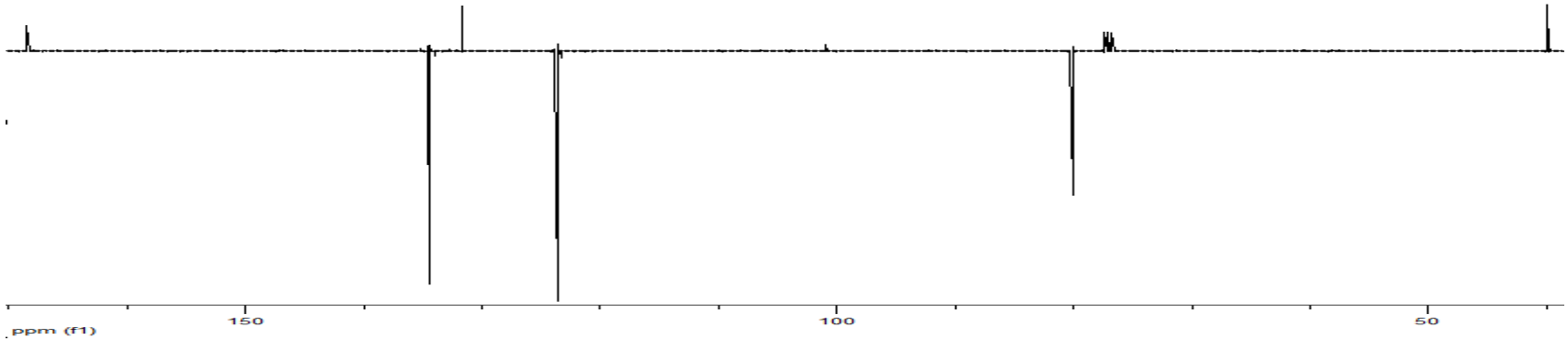
3.70

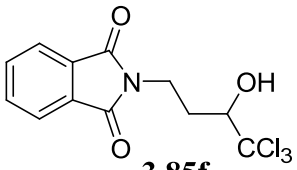




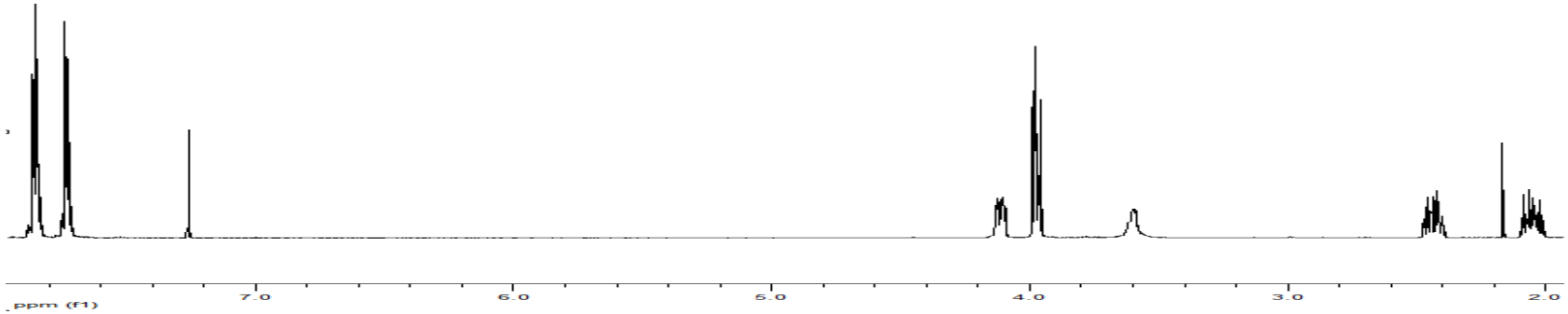
3.85e

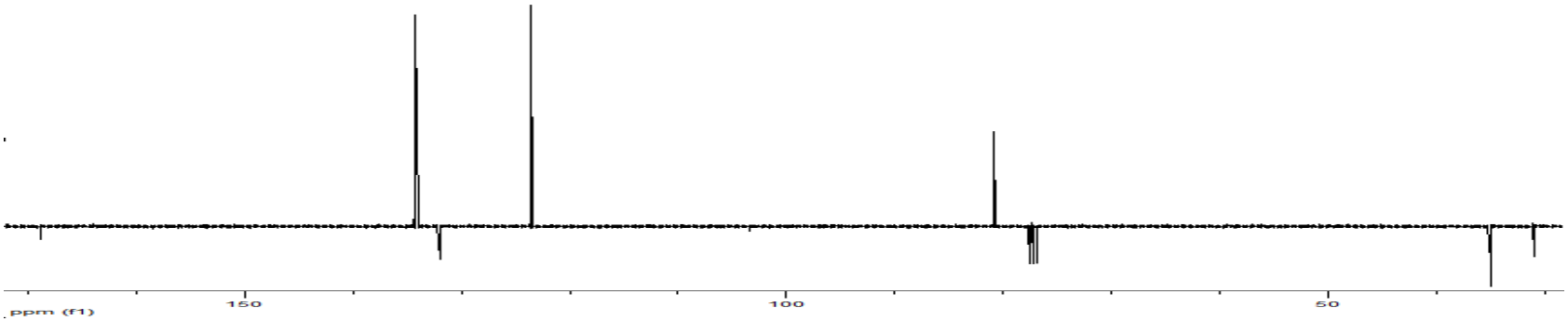


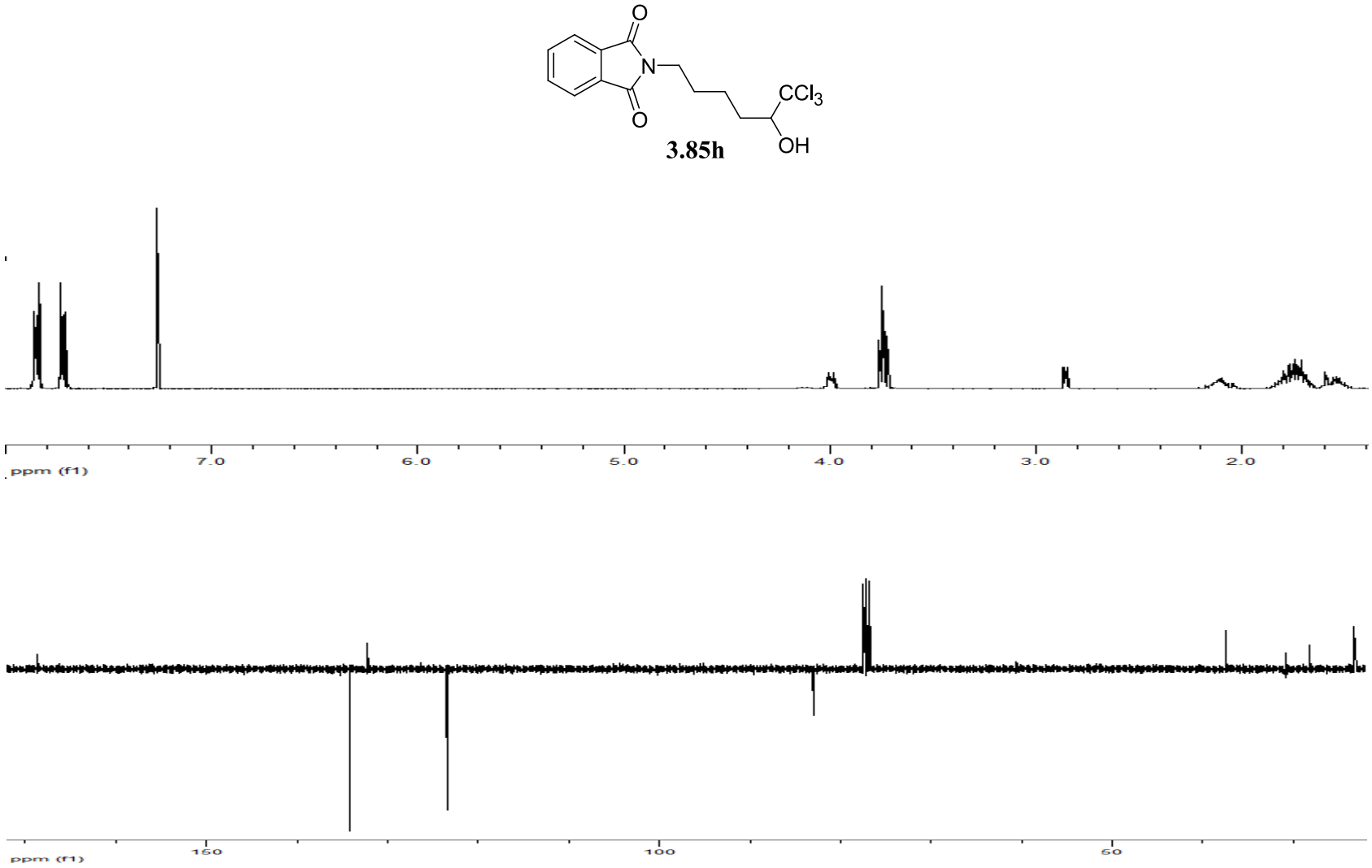




3.85f



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N
O
CCl3
OH
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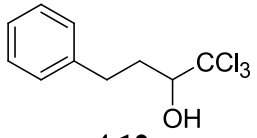
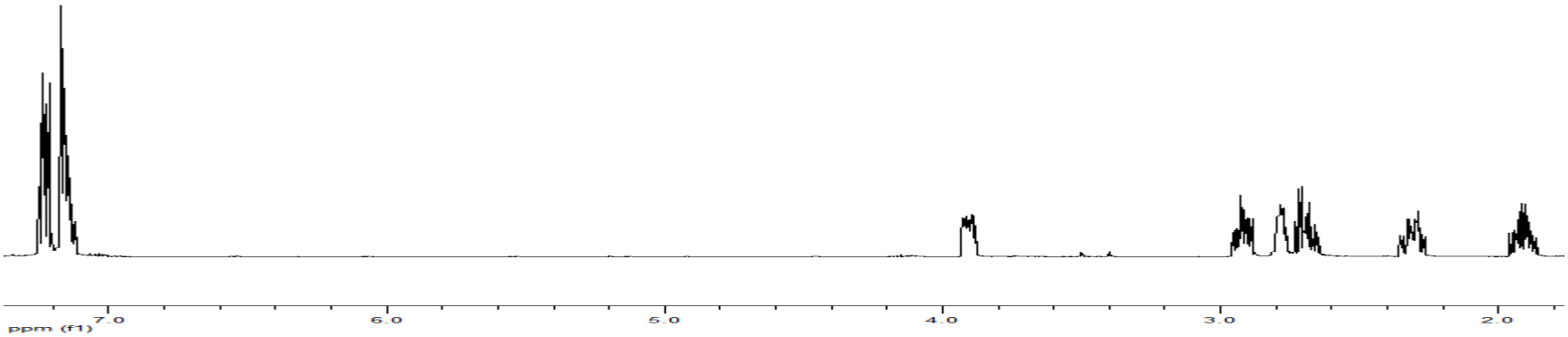
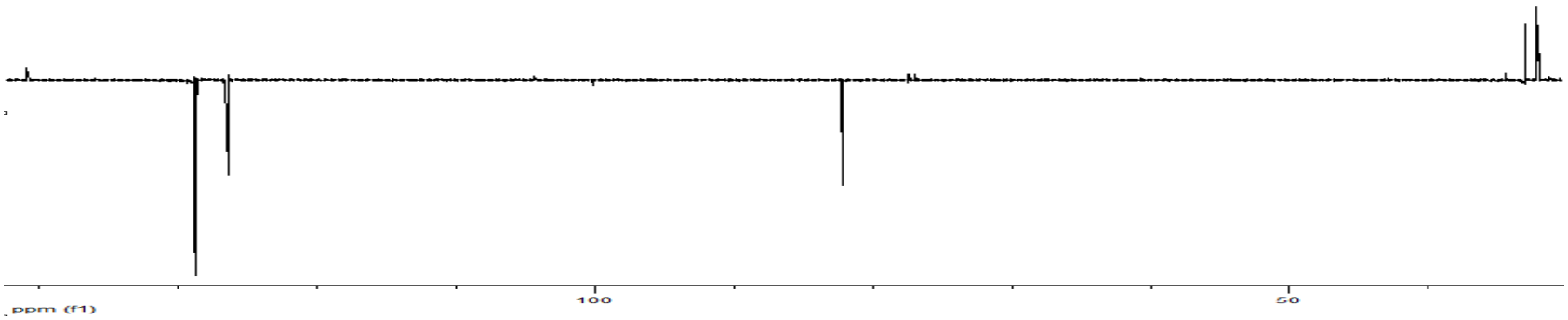
ppm (f1)
7.0
6.0
5.0
4.0
3.0
2.0
ppm (f1)
150
100
50

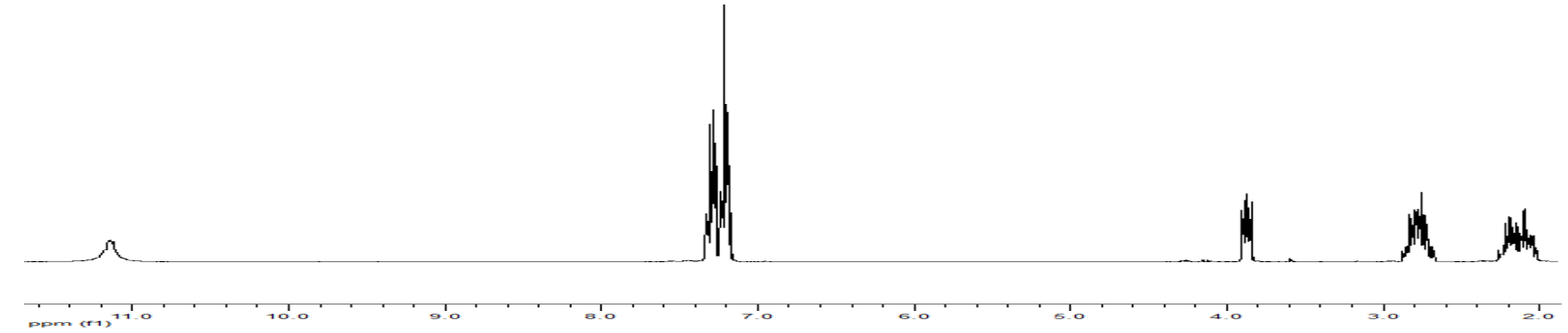


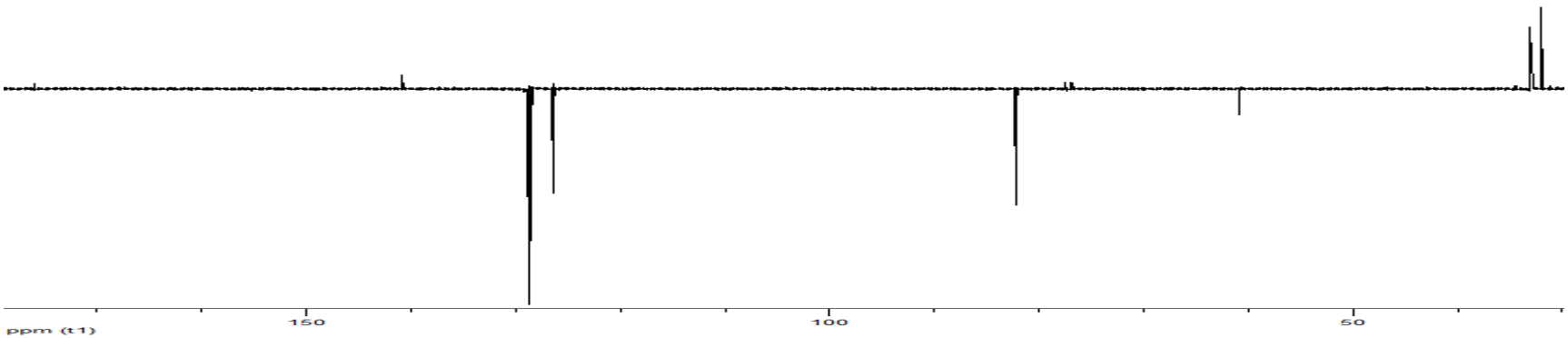
4.12

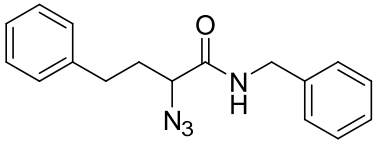




4.13







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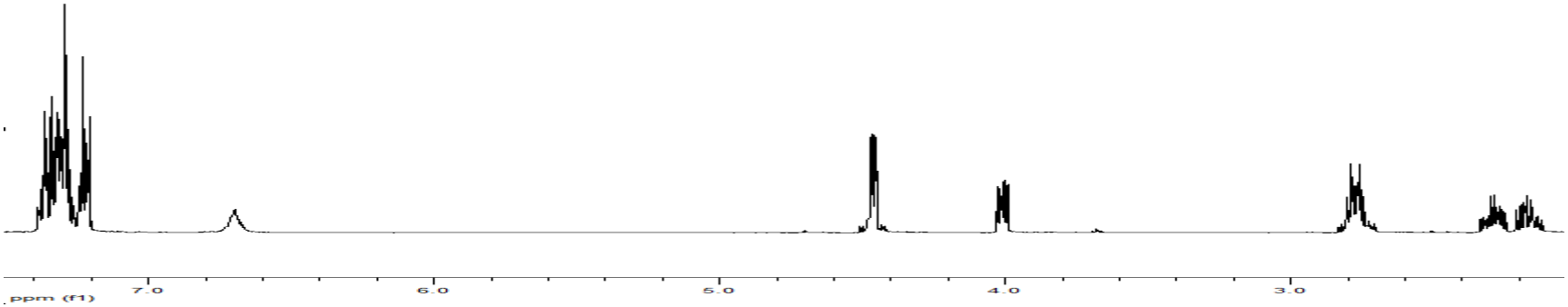

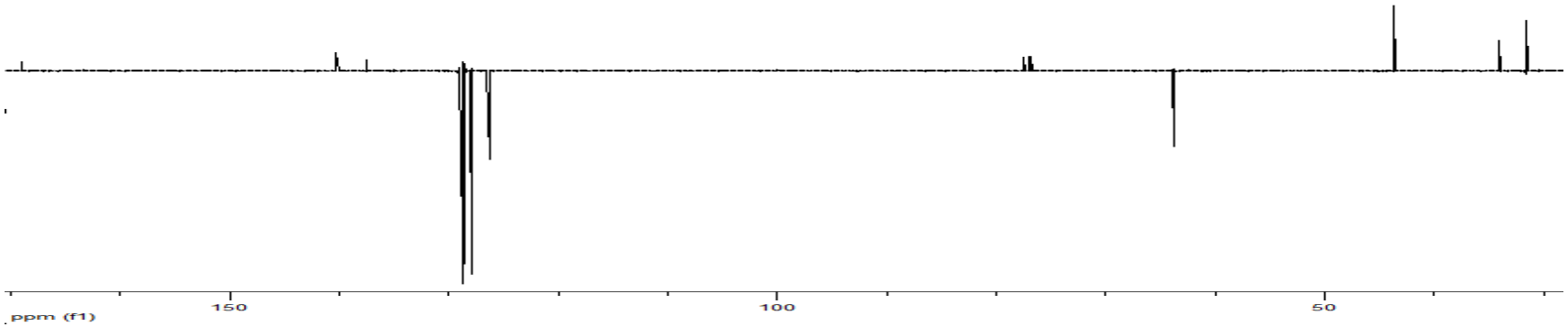

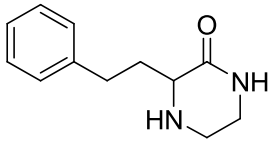

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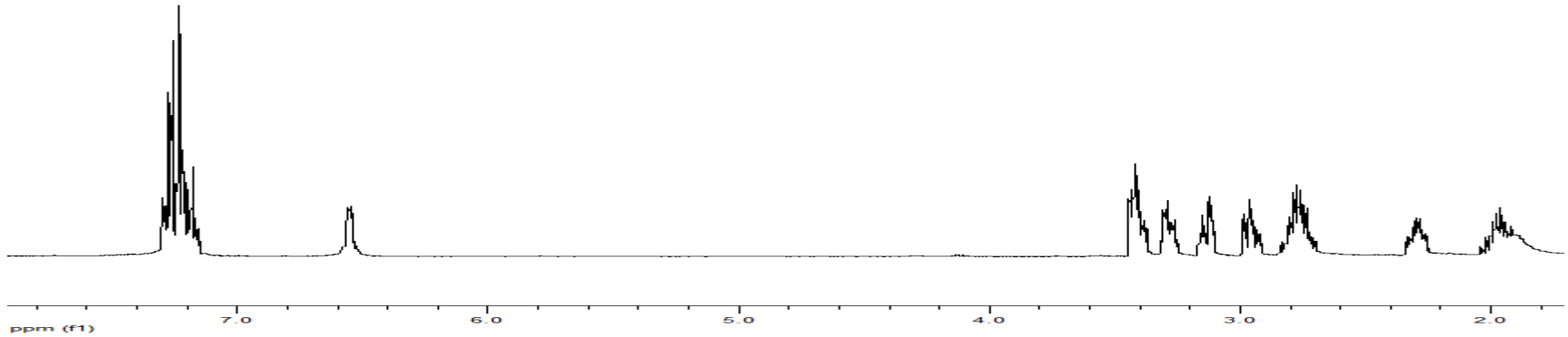

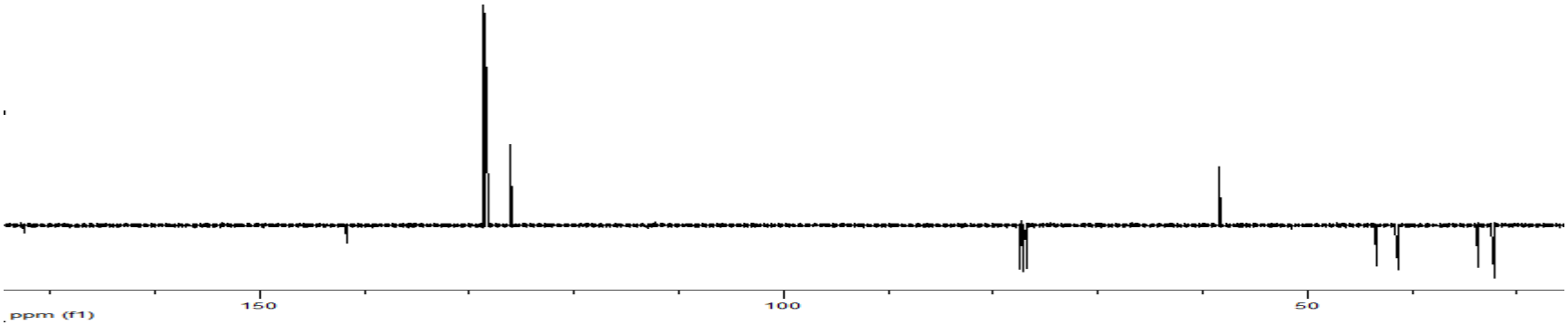

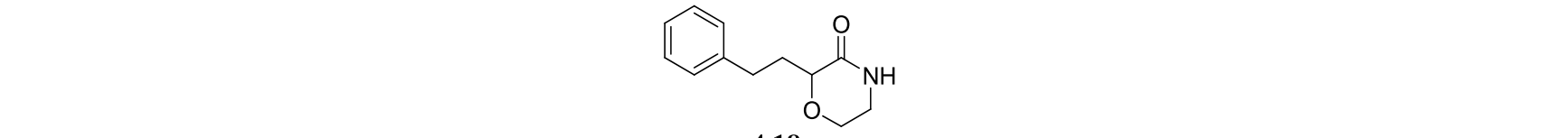

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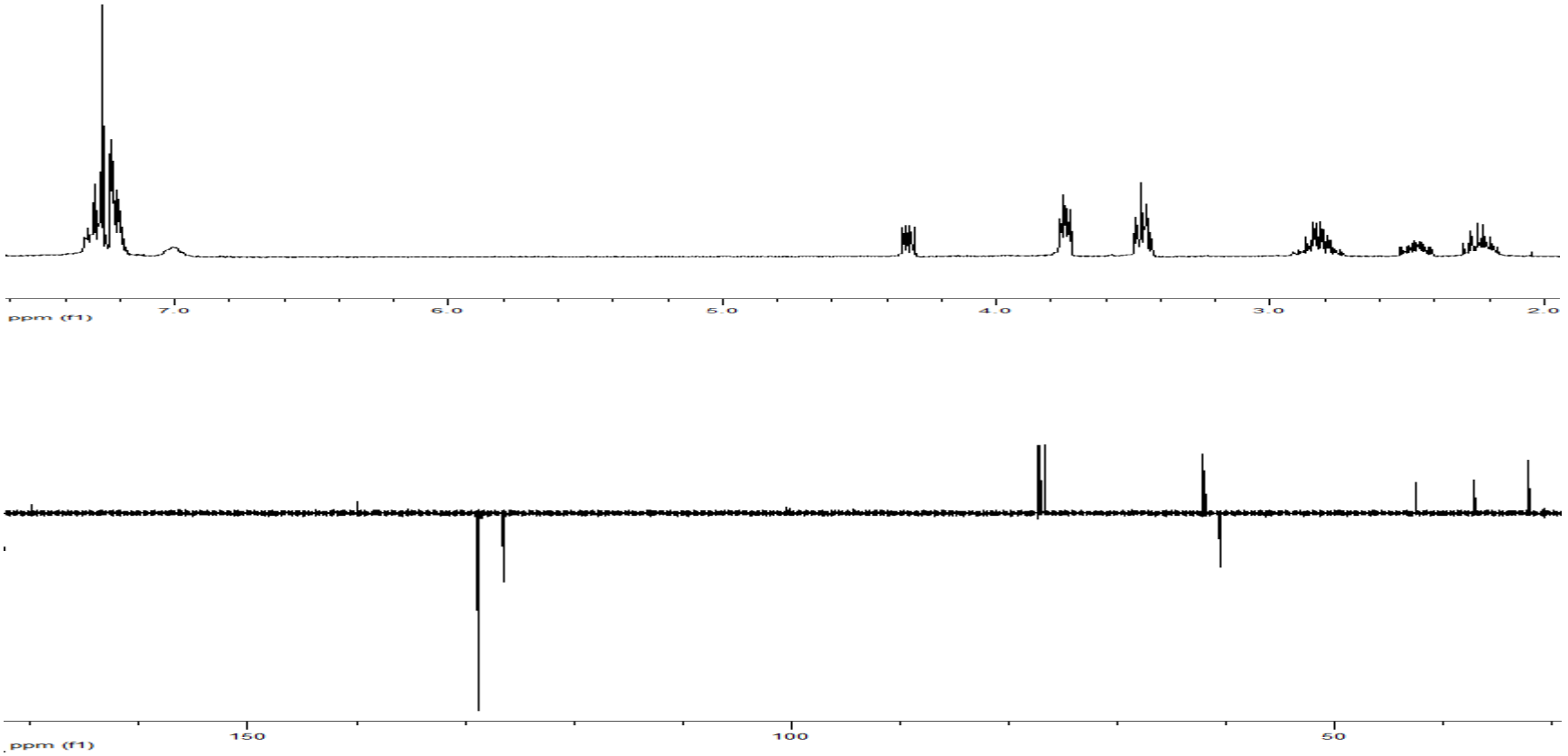

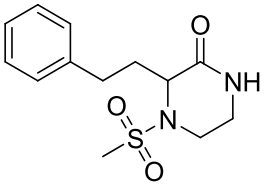

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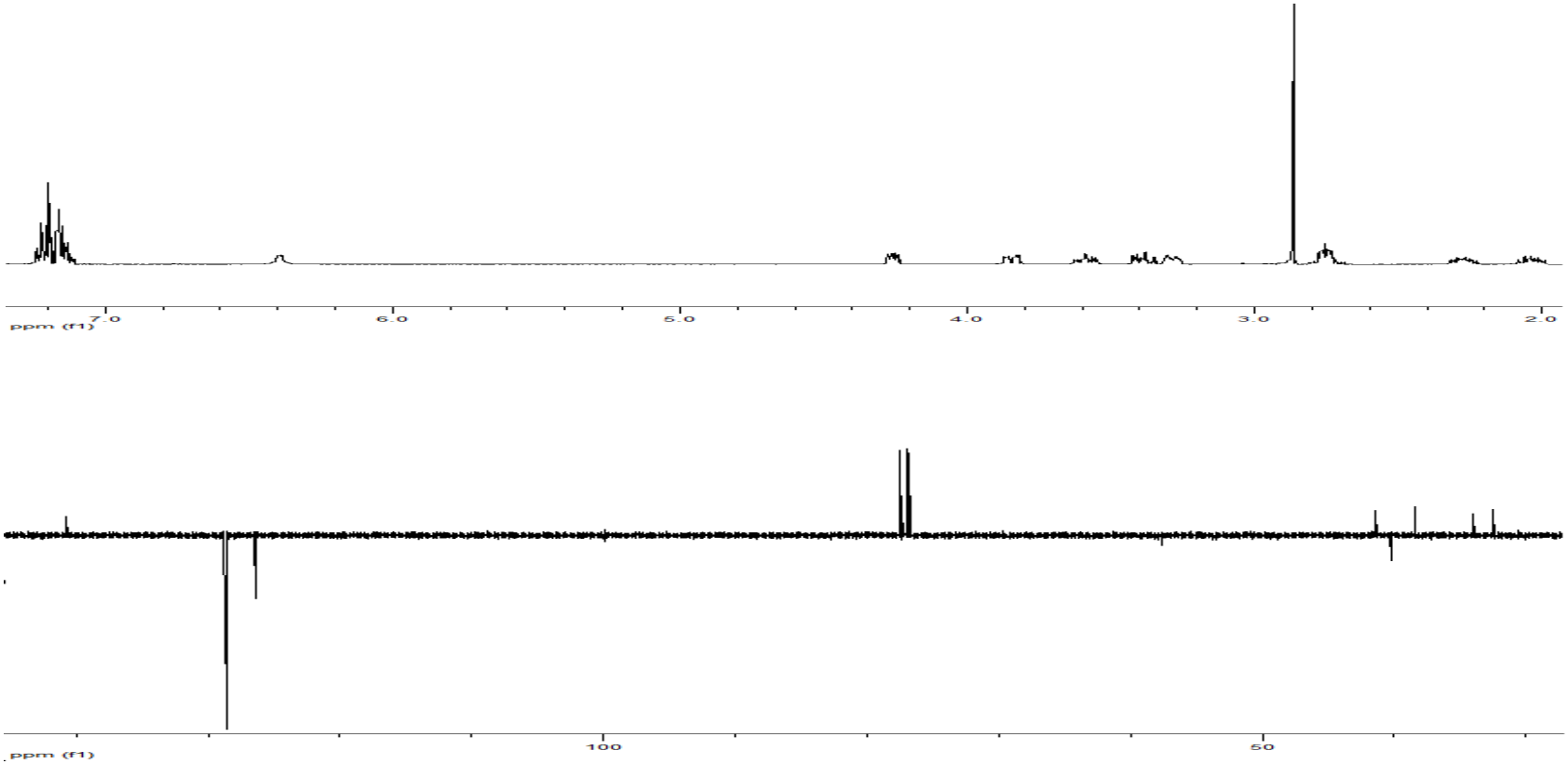

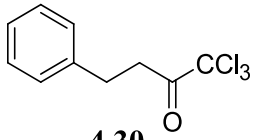

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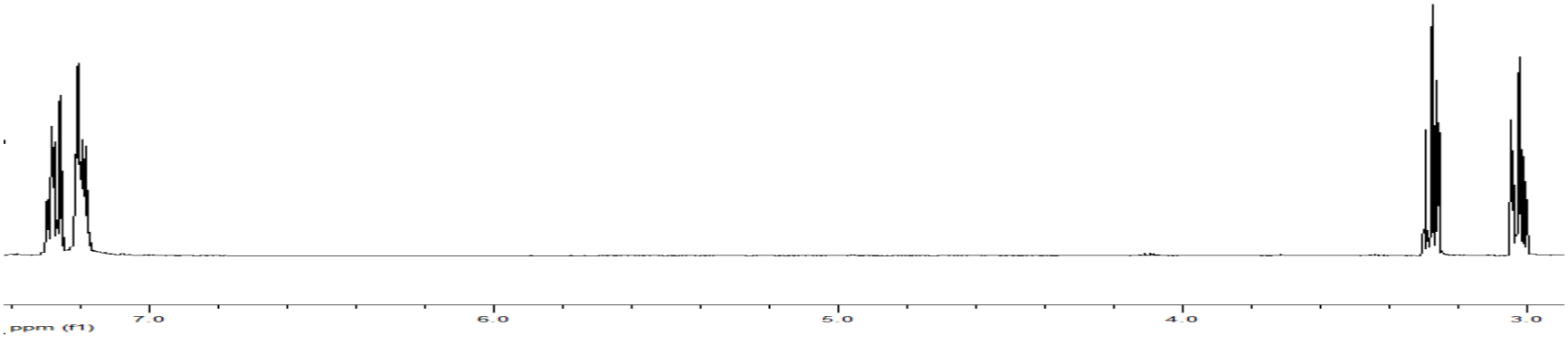

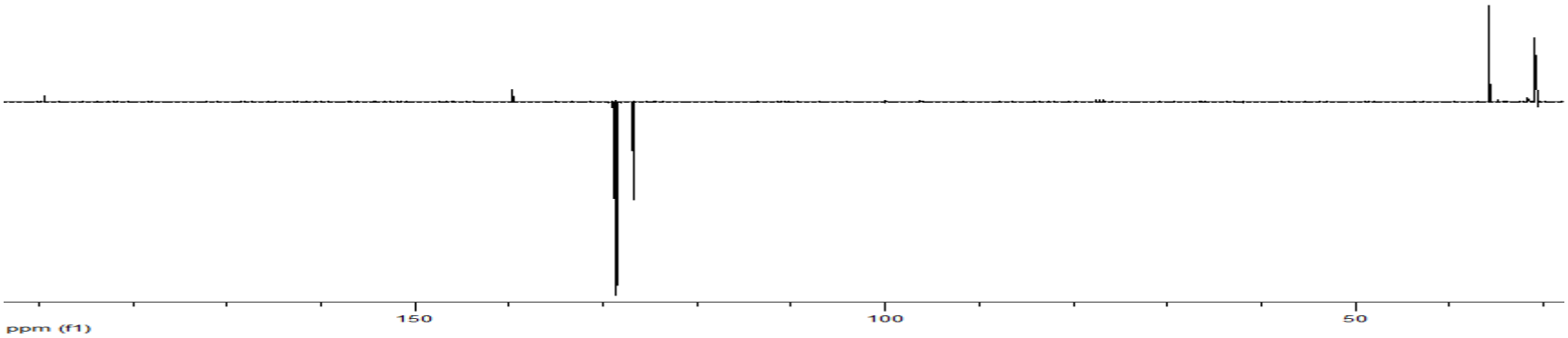

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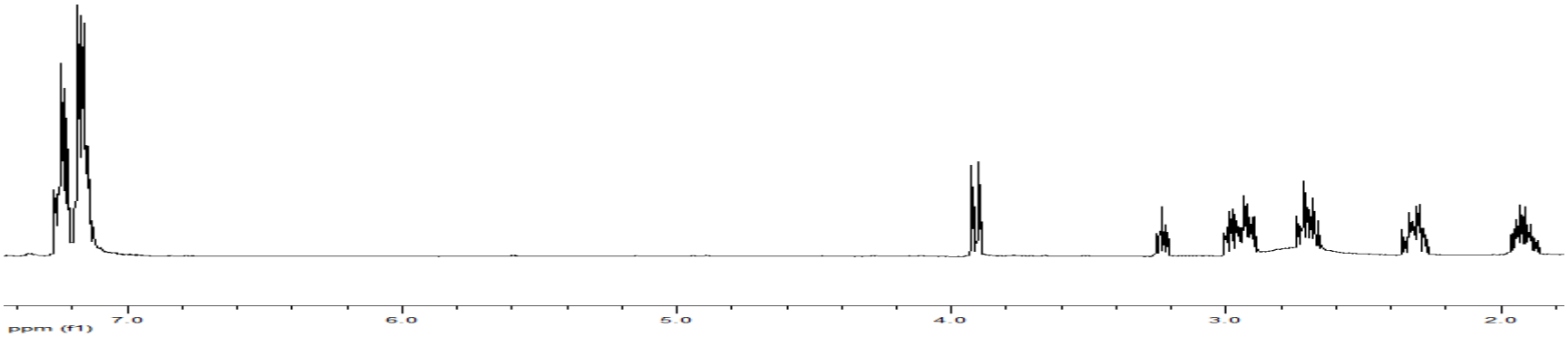

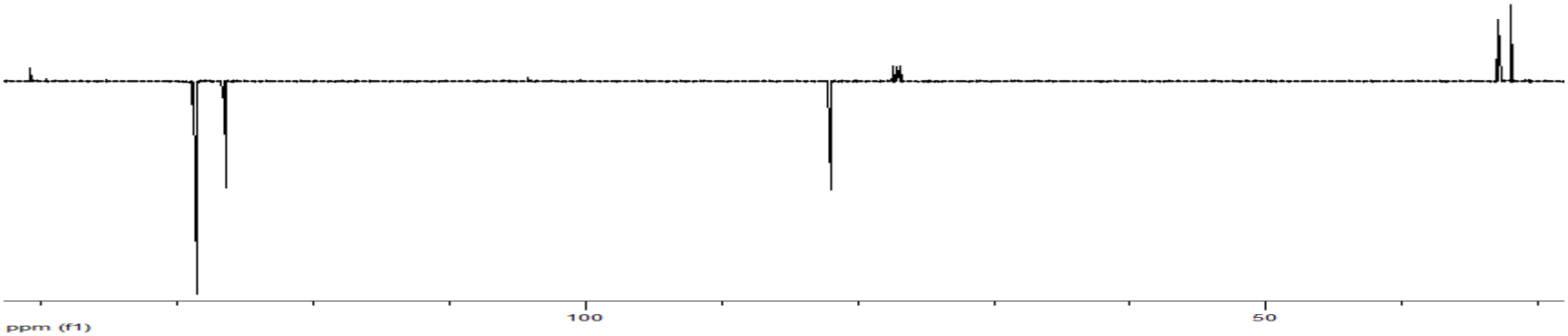

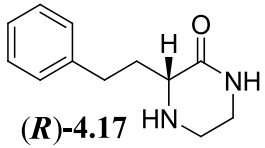

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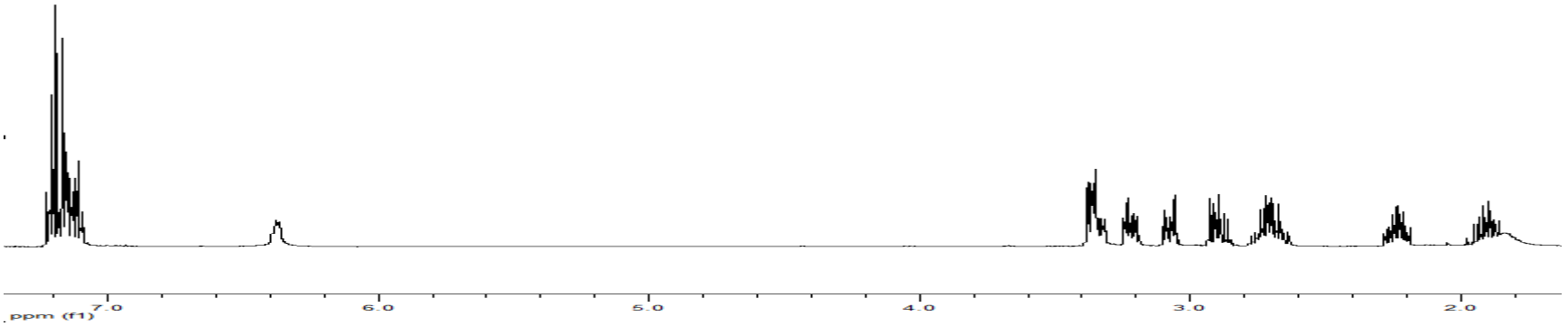
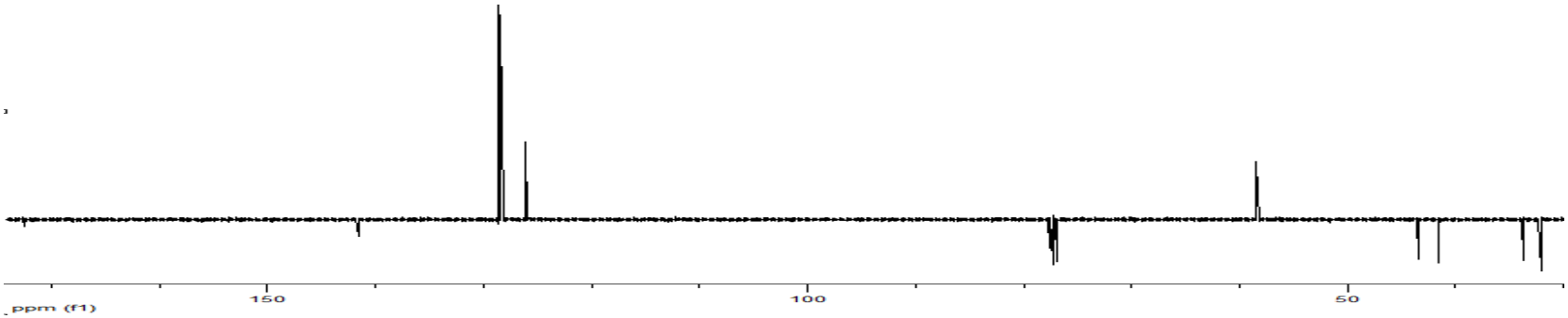
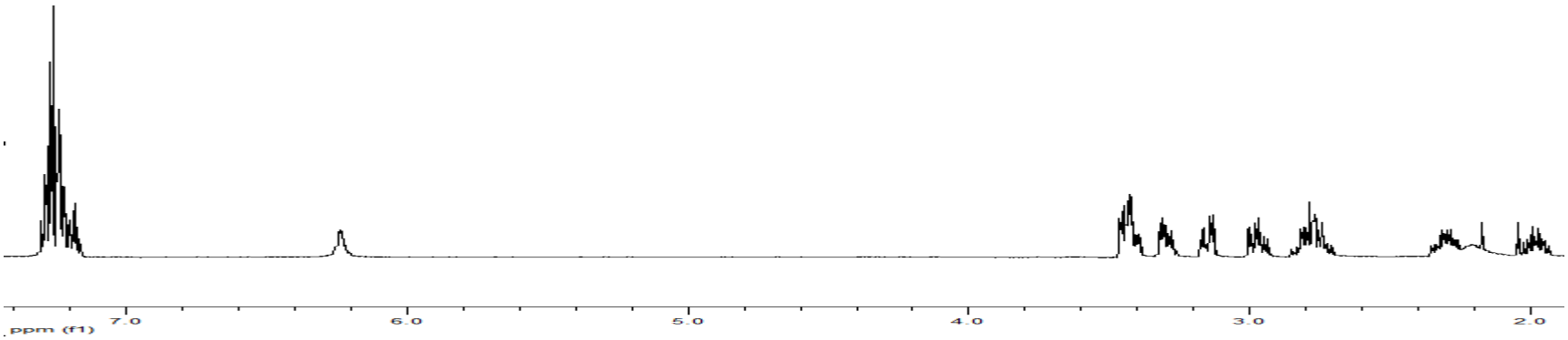
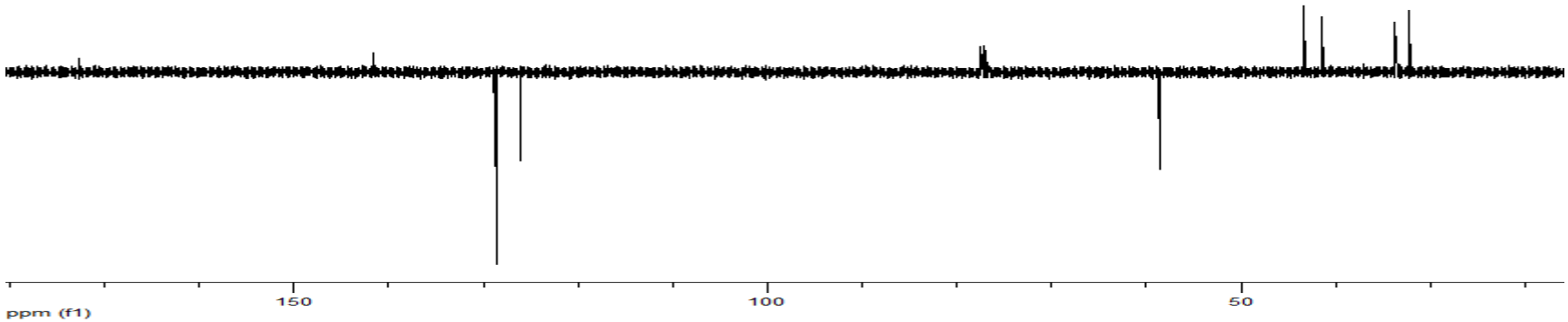
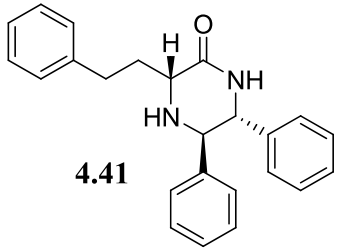




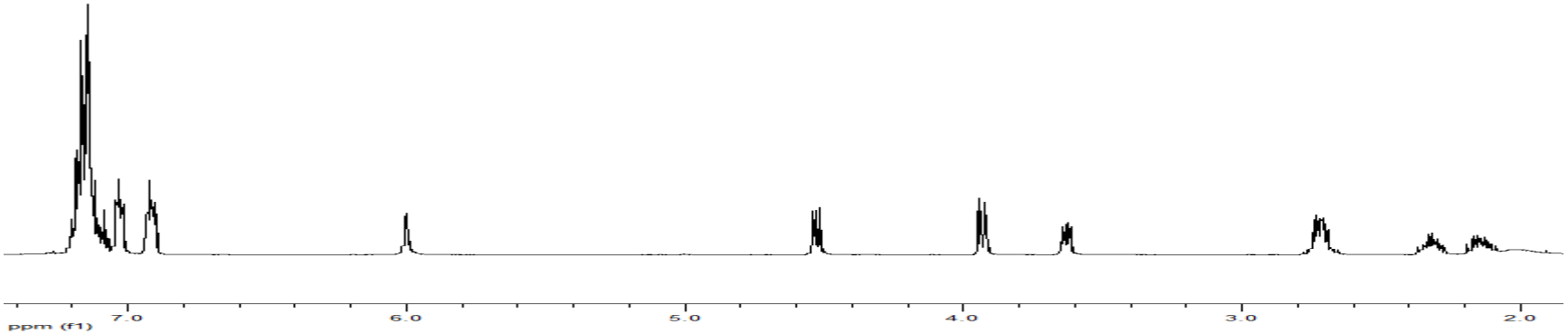
(*S*)-4.17

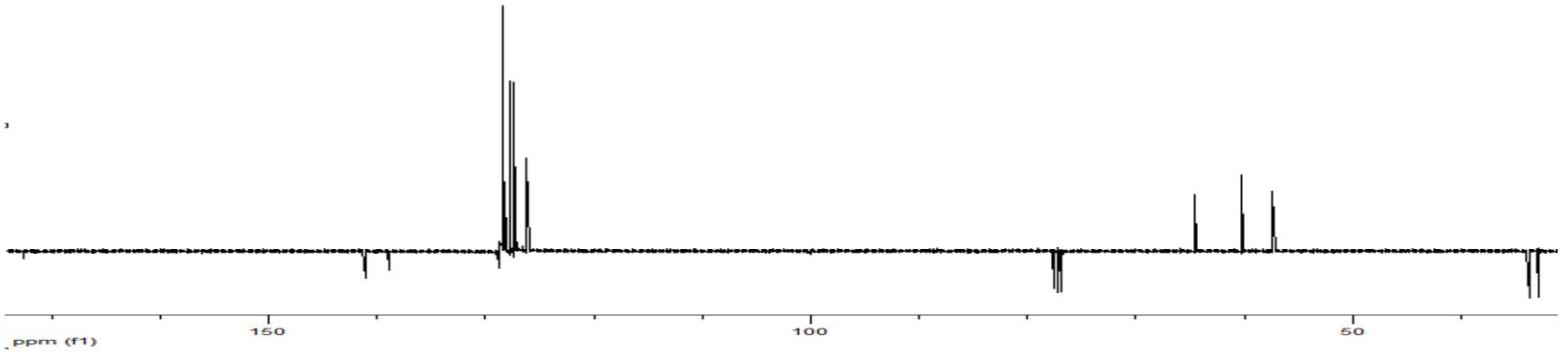


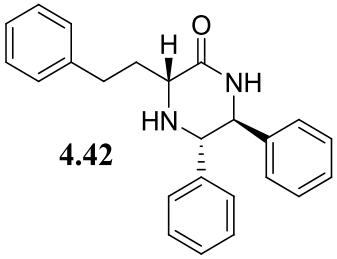




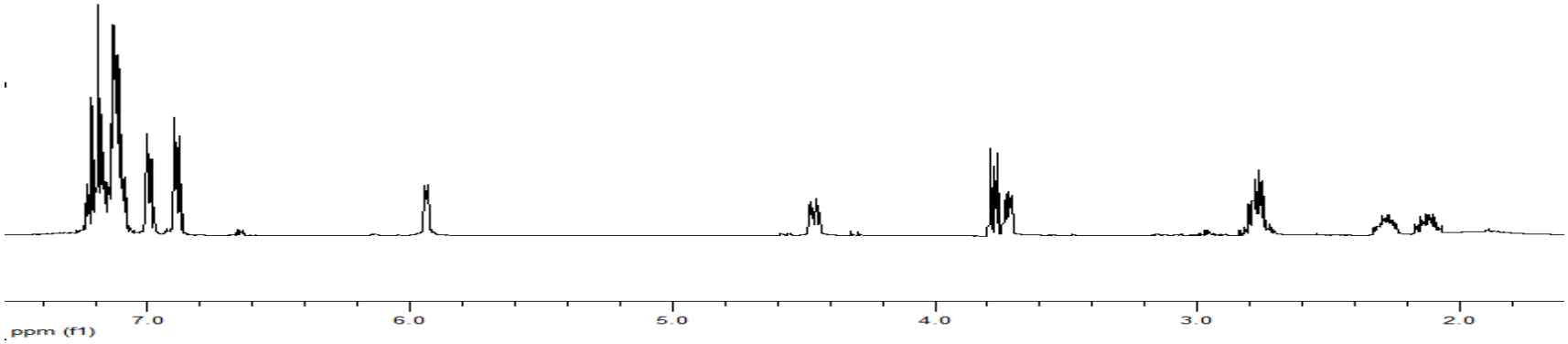
4.41

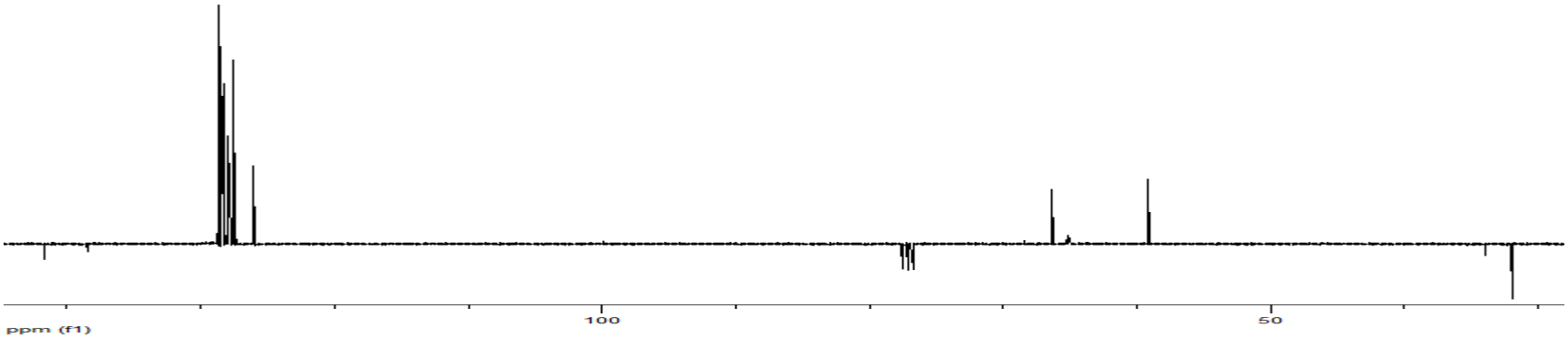






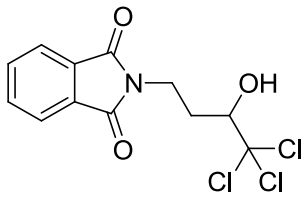
4.42



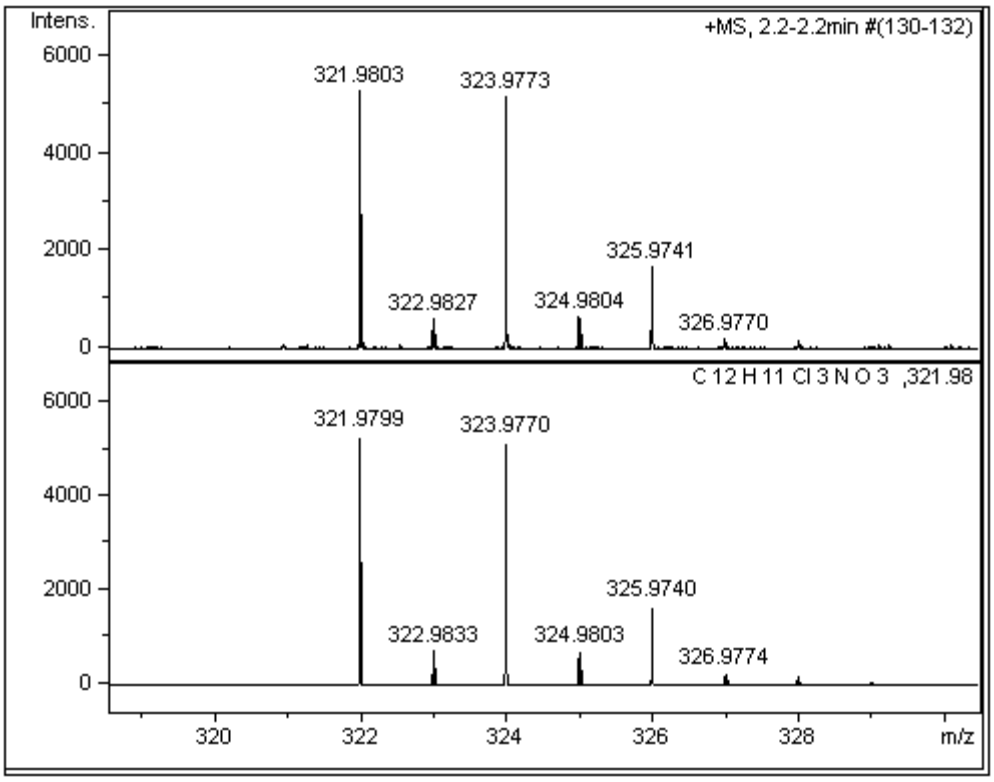


APPENDIX II - Representative High Resolution Mass Spectrum

Representative high resolution mass spectrum taken on a Bruker micro-TOF ESI attached to a time of flight (TOF) analyser.

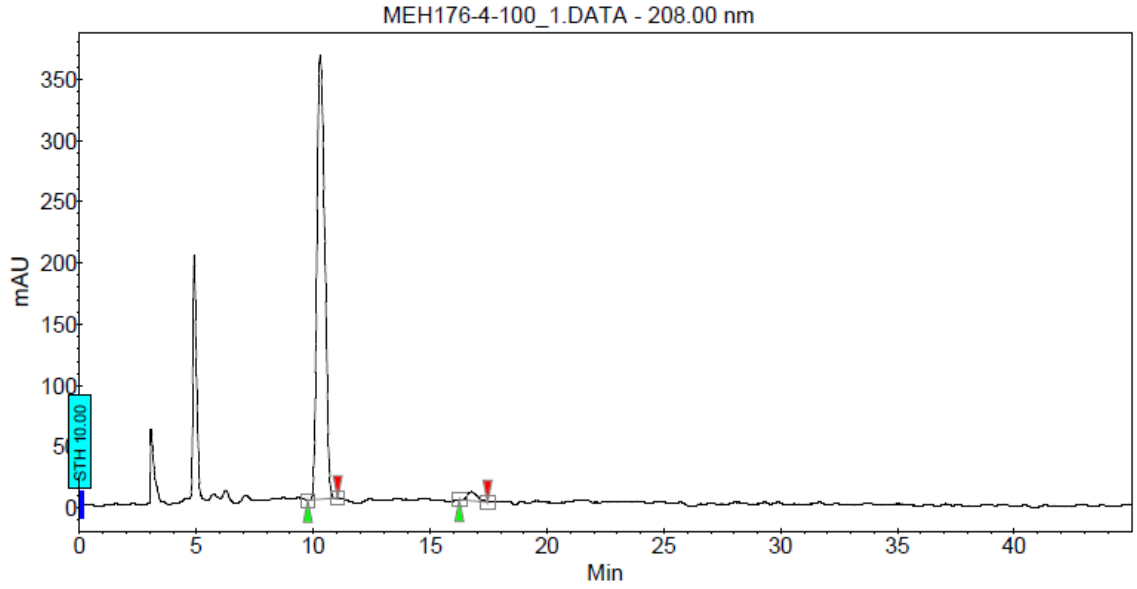


Chemical Formula: $C_{12}H_{10}Cl_3NO_3$
Exact Mass: 320.97
Molecular Weight: 322.57



APPENDIX III - ATH HPLC trace

Representative HPLC trace of the asymmetric transfer hydrogenation reaction, taken from compound **(*S*)-4.12**.



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	10.28	97.57	362.9	141.0	97.571
2	UNKNOWN	16.80	2.43	7.0	3.5	2.429
Total			100.00	369.9	144.5	100.000